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Medium-Sized Rings versus Macrocycles through Rhodium-Catalyzed Ring-Expansion Reactions of Cyclic Acetals

Rafael Ballesteros-Garrido,^[a] Diane Rix,^[a] Céline Besnard,^[b] and Jérôme Lacour*^[a]

Abstract: α -Diazo β -ketoesters and diketones react with cyclic acetals under Rh^{II} catalysis to yield unprecedented polyoxygenated 8- and 9-membered rings in one pot. The reactions occur under mild conditions with yields up to 90%. A perfect regioselectivity is obtained, which can be rationalized through a mechanistic hypothesis that considers 1) the formation of an oxonium ylide, 2) its transformation into an unsaturated acyclic oxocarbenium electrophilic intermediate, and 3) an intramolecular nucleophilic attack in a direct application of Baldwin's rules.

Keywords: carbenoids • diazo compounds • medium-ring compounds • rhodium • ylides

Introduction

Oxonium ylides, which can be prepared by the reactions of singlet carbenes and metal carbenoids with ether molecules, are valuable reactive intermediates.^[1] They undergo a variety of synthetic transformations including [1,2]- and [2,3]-Stevens rearrangements.^[1d,g,2] Products of higher molecular complexity can often be obtained through a series of intraand intermolecular reactions.^[3] For instance, oxonium ylides and small cyclic ethers (with a ring size of six or less) react together and yield polyoxygenated 15- to 22-membered macrocycles in a single pot.^[4] In this context, our group has recently shown that dirhodium-catalyzed decompositions of α -diazocarbonyls 1 in the presence of oxetanes affords 15membered rings of type 2 [Eq. (1)].^[4e] Under virtually the same conditions, 16- or 18-membered rings 3 and 4 are obtained when THF, tetrahydropyran (THP), or 1,4-dioxane are used as solvents instead [Eqs. (2) and (3)].^[4d] These results were rationalized by considering the formation of oxonium ylide intermediates 5-7 and their subsequent dimeriza-



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tion or successive intermolecular reactions with ether molecules. Of importance to the current study, macrocycles 2–4 were

formed as the major products of these reactions. Simpler 7-,

8-, or 9-membered rings of type 8, 9, and 10 [Eqs. (4), (5)

and (6)], which could have resulted from intramolecular re-

actions of nucleophilic and electrophilic sites within ylides 5, 6, and 7, were either not observed or appeared only in trace

amounts.^[4a,5] Herein, in a mechanistic exercise with synthetic applications, the macrocyclic reactivity is directed towards the exclusive formation of analogues of **8**, **9**, and **10**; this was achieved through the direct application of Baldwin's rules^[6] and a modification of the oxo-nucleophiles. In fact, the simple use of cyclic acetals instead of ethers allows the preparation of unprecedented medium-sized 8- or 9-membered rings.^[7]

Results and Discussion

Intermediates 5–7 form either predominantly or exclusively 15-, 16- and 18-membered rings of type 2–4.^[4d,e] The reason for this macrocyclic preference was investigated. The requirement for nucleophilic additions on the oxonium part of the ylide intermediates to proceed through S_N 2-like transition states (i.e., with 180° bond angles between entering and internal leaving groups) was proposed to explain this reactivity.^[8] In other words, in compliance with Baldwin's rules 5, 6, and 7 cannot undergo intramolecular 5-*endo-tet* cyclization reactions due to their constrained geometry;^[6] the accumulation of the observed products 2–4, arises from subsequent dimerization of the intermediates 5–7 or successive intermolecular reactions with ether solvent molecules.

To verify the analysis, we wanted develop a way to bypass the usual reactivity and enforce the synthesis of mediumsized rings. Ideally, this change of reactive pathway would be made possible by a simple modification of the skeleton of one of the two reactive partners — and the cyclic ether moiety in particular. In fact, a change to the sp³ nature of the electrophilic center next to the ether oxygen was required; its tetrahedral geometry tends to enforce S_N2 -like transition states and disfavor n-*endo-tet* cyclization reactions $(n \le 8)$.^[8] As a possible solution, its replacement by a trigonal sp² center was considered because, in this case, n-*endo-trig* cyclization reactions would then be allowed.

Under this working hypothesis, ways to "transform" a tetrahedral sp³ into a trigonal sp² center were looked for. The easiest solution seemed to be the introduction of a second oxygen atom in a 1,3-relationship to the first. Upon reaction with the carbenoid, the cyclic acetal would form an oxonium ylide intermediate (**11**; Scheme 1) that would then collapse into an acyclic derivative **12** through a ring-opening induced by a lone-pair of the second oxygen atom. The resulting intermediate **12** is an oxocarbenium moiety that is ideally suited to undergo n-*endo-trig* cyclization reactions.^[9] In view



Scheme 1. Modification of the reactive pathway towards the exclusive formation of medium-sized rings.

of the availability of 1,3-dioxolane, 1,3-dioxane, and 1,3,5trioxane, it was easy to test the concept using these molecules as solvent or reactant.

We first focused on the reactivity of 1,3-dioxane 13 [Eq. (7)] with α -diazo ketoesters 1a-i and diketones 1j-l (Scheme 2); the results are summarized in Table 1. The reactions were performed under conditions similar to those



Scheme 2. Diazo compounds 1 selected for the study.

already reported with 1,4-dioxane.^[4d] For instance, ethyl diazoacetoacetate 1a was added at 60°C to a solution of $[Rh_2(OAc)_4]$ (1.0 mol%). The reaction was over in less than 2 h. NMR spectroscopic analysis of the crude reaction mixture indicated the formation of a single product 14a; a new cyclic derivative was isolated in 72% yield (Table 1, entry 1). To our satisfaction, through mass spectrometry (ESI: m/z 216.1 [M+H⁺]), IR (1628 cm⁻¹), and detailed NMR (HMBC, HSQC) analyses, an enediol acetal structure of type 14 was ascertained; the connectivity and 9-membered ring structure of which was confirmed by X-ray diffraction analysis (see Figure 1 below). The origin of the perfect regioselectivity will be discussed later.^[10] In terms of synthesis, $[Rh_2(Oct)_4]$ and $[Rh_2(OAc)_4]$ behaved similarly; however, the latter, being less expensive, was preferred for further studies. Performing the reaction at 0.5 and 1.0 M concentrations of 1a gave the same results. However, because [Rh₂(OAc)₄] is only partially soluble at a concentration of 1.0 M, further reactions were performed using 0.5 M of diazo reagent.

Variations on the ester side chains were investigated $(R^1 = OMe, OCH_2(3,5-F_2C_6H_3), OtBu)$, resulting in the formation of analogous derivatives **14b**, **14c**, and **14d**. Although spectroscopic evidence indicated that these com-







[a] Reagents and conditions (Procedure A): 1a-i (1 equiv), 0.5 M in 13 or 15 as solvent, $[\text{Rh}_2(\text{OAc})_4]$ (1 mol %), 2 h, 60 °C. [b] Isolated product yield after filtration over neutral alumina. [c] Reagents and conditions (Procedure B): 1a-i (1 equiv), 17 (20 equiv), $[\text{Rh}_2(\text{OAc})_4]$ (1 mol %), toluene (0.2 M), 2 h, 60 °C. [d] 25 °C, 12 h.

pounds were formed as the sole products of the reactions, they were, however, isolated in only moderate yields (40, 41, and 37% respectively; Table 1, entries 2–4). The low isolated yields were attributed to an acute volatility and a sensitivity to the chromatographic purification conditions.

Further variations were performed with allylic and homobenzylic derivatives **1e** and **1f**. These reactants are known to undergo intramolecular cyclopropanation^[11] and CH insertion^[12] reactions under dirhodium catalysis; reactions that should compete with the process under investigation. When the crude mixtures were examined, product **14e** (30%) was found to be present along with the bicyclic [3.1.0] lactone **15** [8.3:1.0 ratio, Eq. (8)].^[13] With **1f**, medium-sized ring compound **14f** (14%) was also found to predominate [2.0:1.0 ratio with the monocyclic lactone **16**, Eq. (9)]. These two ex-



FULL PAPER

amples show that the "intermolecular" cyclization procedure competes favorably with wellestablished intramolecular reactions.

Phenyl and *n*-propyl substituents were then introduced α to the carbonyl group of the diazo reagent (Table 1, entries 7 and 8). The expected products 14g and 14h were, however, obtained in only 19 and 13% yield, respectively. In this series, steric hindrance impedes the reaction to a greater extent.^[14] Coumarine derivative 1i was then tested. Usually, in this type of reaction, this substrate behaves differently from other α-diazo ketoesters.^[4b] However, no such difference was observed in this case, and the corresponding 9-membered ring compound 14i was obtained as a single product (46% yield; Table 1, entry 9). This derivative was found to be moderate-

ly soluble in heptane and a slow diffusion of this solvent into a solution of **14i** in dichloromethane afforded X-ray quality crystals. A structural analysis was performed that unambiguously confirmed the 9-membered ring structure and also the regioselectivity of the reaction (Figure 1); the acetal group indeed being linked to the oxygen atom belonging to the former carbonyl group.



Figure 1. ORTEP view of the crystal structure of **14i**. Thermal ellipsoids are drawn at 50% probability.

Finally, the reaction was performed with more reactive diazodiketones **1**j–l (Table 1, entries 10–12). The corresponding products were obtained in moderate to good yields (**14**j, **14k**, and **14l** in 40, 67, and 77 % yields, respectively). With reactants **1k** and **1l**, it was necessary to decrease the reaction temperature to 25 °C because side products **17k** and **17l** were observed at 60 °C. According to NMR analyses, these products arise from C–H insertion reactions (Scheme 3), which, interestingly, present a regioselectivity different to

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Scheme 3. Competition between 9-membered ring 14k-l formation and C-H insertion reactions.

that usually observed.^[15] Unfortunately, these adducts decomposed upon purification.

Having established this set of results by employing 1,3-dioxane 13, we turned our attention to the use of 1,3-dioxolane 18 as reactant, expecting little differences in reactivity [Eq. (10)]. In fact, rather similar results were obtained using the previously developed conditions (diazo (0.5 M), [Rh₂(OAc)₄] (1.0 mol%), 60 °C, 2 h). In all cases, trioxo 8membered rings of type 19 were isolated from the reactions of diazo compounds 1a–1. As for the previous series, composition and regiochemistry were established by spectrometric, spectroscopic, and X-ray diffraction analyses. The solid state structure of 19 i is depicted in Figure 2.



Figure 2. ORTEP view of the crystal structure of **19***i*. Thermal ellipsoids are drawn at 50% probability.

Globally, the reactions performed equally well or better with 1,3-dioxolane, with those involving diazo compounds **1a**, **1d**, **1e**, **1f**, and **1i**, in particular (see Table 1); in these cases, isolated product yields were improved by at least 18%. Products **19e** and **19f** were isolated in 57 and 56% yields, respectively (instead of 30 and 14% for **14e** and **14f**). The reason for these improved yields was due to the absence of competing cyclopropanation or CH insertion reactions. Finally, diazo compounds **1j–1** were reacted in 1,3dioxolane and the corresponding products were obtained in moderate to good yields (**19j**, **19k**, and **191** yields 46, 68, and 77%; Table 1, entries 10–12). Interestingly, no side products were detected even at 60°C.

Following these precedents, compounds of type 20 bearing four (instead of three) oxygen atoms in the medium-sized ring were also prepared. Reactions were performed using solutions of 1,3,5-trioxane **21** (20 equiv) in toluene as solvent [Eq. (11)]. In essentially all cases,^[16] the corresponding 9membered rings were isolated (31–85%; Table 1). As for compounds **14** and **19**, lower yields were usually caused by volatility and a sensitivity of the products towards the purification conditions because crude reaction mixtures contained essentially a single adduct.^[17] Furthermore, as for the previous two series, X-ray quality crystals were obtained from the coumarin-derived adduct and a structural analysis of **20** i was performed. The result, which is shown in Figure 3, clear-



Figure 3. ORTEP view of the crystal structure of **20i**. Thermal ellipsoids are drawn at 50% probability.

ly shows the unique 9-membered ring structure with the three acetal moieties in a row.

These results indicate that the initial mechanistic hypothesis is correct. Most likely, the reaction pathway involves the generation of an electrophilic metal carbenoid of type **22** (Scheme 4). Nucleophilic attack of an oxygen atom from the cyclic acetal generates the corresponding oxonium ylide of type **11**. In the three cases studied, the lone-pair of the unbound oxygen atom provokes an opening of the acetal ring leading to the formation of unsaturated oxocarbenium ions



Scheme 4. Mechanistic proposal.



FULL PAPER

of type 12.^[18] As discussed previously, this trigonal sp² center is now amenable to intramolecular nucleophilic attack, in this case from the carbonyl oxygen atom, leading to the medium-sized cyclic products. In addition, this rationale fully explains the regiochemistry observed in the reactions and the perfect selectivity.

Finally, to further examine the details of the reaction, reactions were performed with unsymmetrical 4-methyl-1,3-dioxane 23 and 4-methyl-1,3-dioxolane 24; the presence of the extra methyl group leading to possible regioisomeric adducts (Scheme 5). Interestingly, in the case of 23, a single regioiso-



Scheme 5. Reactions in the presence of 4-methyl-1,3-dioxane (23) and 4-methyl-1,3-dioxolane (24).

mer 25 was formed during the reaction; the structure of which was assigned by NMR spectroscopic analysis. A similar result was obtained for the reaction with 24, although a minor isomer could be detected in the crude reaction mixture (92:8 regioisomeric ratio). Clearly, and not surprisingly, these results indicate that the less-hindered oxygen atom (without the adjacent alkyl substituent) reacts first with the electrophilic metallocarbene. The second oxygen atom, next to the methyl group, then helps generate the electrophilic oxocarbenium intermediate that is trapped to form the products with the observed regioselectivity. These results demonstrate that steric hindrance plays a role in the initial oxonium ylide formation.^[19]

Conclusion

An original strategy for the one-pot synthesis of polyoxygenated 8- and 9-membered rings has been presented. The approach features an unusual [Rh2(OAc)4]-catalyzed reactivity of α -diazo β -ketoesters and diketones with cyclic acetals. The reactions occur under mild conditions with yields up to 90% to form unprecedented medium-sized rings. A perfect regioselectivity was obtained due to the formation of oxonium-ylide intermediates and their selective transformation into unsaturated acyclic oxocarbenium electrophiles. Intramolecular nucleophilic attacks can then occur readily to afford the eight- and nine-membered rings in a direct application of Baldwin's rules. Further applications of this approach are underway.

Experimental Section

General Procedure A with 1,3-dioxolane (13) and 1,3-dioxane (18): In a 1 mL screw-cap vial equipped with a magnetic stirring bar, $[Rh_2(OAc)_4]$ (5.0 mM solution in 1,3-dioxane or dioxolane (flushed with argon), 0.640 mL) was added in one portion to the diazo compound (0.32 mmol). The reaction vial was then flushed with argon and capped. The reaction was stirred at 60°C and monitored by thin-layer chromatography (TLC, neutral alumina). Upon completion, the reaction mixture was analyzed and then purified on a short chromatography column (neutral Al₂O₃).

General Procedure B with 1,3,5-trioxane 21: In a 3 mL screw-cap vial equipped with a magnetic stirring bar, a solution of trioxane (6.4 mmol) and [Rh₂(OAc)₄] (0.0032 mmol) in toluene (1.750 mL; flushed with argon) was added in one portion to the diazo compound (0.32 mmol). The vial was flushed with argon and capped. The reaction was stirred at 60°C and monitored by TLC (neutral alumina). Upon completion, trioxane was removed under reduced pressure and the reaction mixture was then analyzed and purified on a short chromatography column (neutral Al_2O_3).

CCDC-857512 (14i), CCDC-857513 (19i), and CCDC-857514 (20i) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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CHEMISTRY

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FULL PAPER



Medium rings: α -Diazo β -ketoesters and diketones react with cyclic acetals under Rh^{II} catalysis to yield unprecedented polyoxygenated 8- and 9-membered rings in one pot (see scheme).

The reactions occur under mild conditions with yields up to 90%. The medium-sized ring formation and perfect regioselectivity are direct consequences of Baldwin's rules.

Medium-Ring Compounds

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Medium-Sized Rings versus Macrocy-cles through Rhodium-Catalyzed Ring-**Expansion Reactions of Cyclic Acetals**

