

Organic Synthesis |Hot Paper|

Water Freezing as a Regiocontrol Element in the Multicomponent Assembly of Cyclic Enones

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Abstract: Regioselective synthesis of dialkoxy 2-cyclopentenones and 2-cyclohexenones with novel substitution patterns has been accomplished by the one-pot combination of three simple starting materials (chromium carbene complex, Weinreb acetamide lithium enolate and 1-alkoxyallenyllithium) under either anhydrous conditions or water-promoted solidification of the reaction mixture. These results revealed an unprecedented water-freezing effect that plays a key role to completely reverse the regioselectivity of the intramolecular carbometalation of an allene moiety.

The sequential coupling reaction of a Fischer carbene complex, a lithium enolate and an unsaturated organomagnesium reagent represents a multicomponent cyclization process that is able to rapidly generate molecular complexity and diversity in a single synthetic operation.^[1,2] This basic concept has proved to be a useful strategy for the modular generation of small organic molecules. The first examples of this multicomponent synthetic technique were achieved in our group and allowed the diastereoselective synthesis of pentasubstituted cyclopentanols or tetrasubstituted 1,4-cyclohexanediols by combination of a chromium alkoxycarbene complex, a ketone or ester lithium enolate and allylmagnesium bromide.^[3] More recently, we have described the enantioselective synthesis of 4-hydroxy-2cyclohexenones^[4] and 6–5 bicyclic γ -alkylidene-2-butenolides^[5] by coupling of a methoxycarbene complex of chromium, a chiral non-racemic imide lithium enolate and an initially prepared propargylic organomagnesium reagent. In this context, we became interested in developing new multicomponent cyclization methodologies by using amide lithium enolates which would allow the introduction of a ketone carbonyl group in the corresponding cyclic structure. Here we report the successful reaction of a Fischer carbene complex with an amide lithium enolate and then with an 1-alkoxyallenyllithium that selectively provides five- or six-membered-ring conjugated enones depending on the reaction conditions (Scheme 1). In addition, we communicate an unprecedented water-freezing effect that promotes a total inversion of the regioselectivity in the cyclization step.

Cyclic enones are both high-value building blocks in organic synthesis and key structural features in various biologically active natural products and pharmaceuticals.^[6] Although numerous strategies for the preparation of substituted cyclopenten-2-ones^[7,8] and cyclohexen-2-ones^[9,10] are already available, the development of new and more efficient methods for the

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munication

Scheme 1. Three-component synthesis of novel 2-cyclopentenones and 2-cyclohexenones by sequential coupling of three starting materials.

synthesis of these significant families of compounds constitutes an important ongoing challenge. In this report, we disclose a complementary and selective multicomponent construction of two types of cyclic conjugated α -alkoxyenones with a unique substitution pattern.

Improvements in terms of reaction rate and efficiency have been reported by high pressure induced by external waterfreezing or frozen solvent conditions.^[11] But, as far as we are aware, the change of the reactivity of an organometallic intermediate as a consequence of the solidification of the reaction mixture by water addition at low temperature (water-freezing effect) is unknown.

For the preliminary experiments we chose *N*-methoxy-*N*-methyl amides (Weinreb amides, well-established as effective acylating agents)^[12] and lithiated alkoxyallenes. Lithium enolate **2** was prepared by treatment of *N*-methoxy-*N*-methylaceta-mide with either lithium diisopropylamide (LDA; THF, -78° C, 30 min) or *t*BuLi (THF, -78° C, 1 h).^[13a] 1-Alkoxyallenyllithiums **3** were generated from the corresponding 1-alkoxyallene and BuLi (THF, -78° C, 30 min).^[14] Thus, the successive reaction of a chromium methoxycarbene complex **1** with Weinreb acetamide lithium enolate **2** and then with an 1-alkoxyallenyllithium **3 a,b** conducted under the reaction conditions summarized in Table 1, led selectively, after hydrolysis and decoordination



-78 °C, 30 min; -55 °C, 12 h and then 20 °C, 15 min. Lithium enolate **2** was prepared from *N*-methoxy-*N*-methylacetamide and LDA (THF, -78 °C, 30 min). [b] Yield of isolated, analytically pure product based on carbene complex **1**. [c] In this reaction lithium enolate **2** was generated by treatment of *N*-methoxy-*N*-methylacetamide with *t*BuLi (THF, -78 °C, 1 h).



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of the metal species by exposure to air and light, to the corresponding 2,4-dialkoxy-2-cyclopentenone **4**. This reaction proceeded very efficiently with different carbene complexes **1a–f** and presented a good generality (R¹ group = aryl, heteroaryl, alkenyl and alkynyl). The reaction of amide enolate **2** with carbene complexes **1** occurs almost immediately at low temperature (-78 °C). Allenyllithium reagent **3** was added at -78 °C and after keeping the reaction mixture at -55 °C overnight, it was allowed to warm to room temperature before hydrolysis (NH₄Cl/H₂O). When prior to this hydrolysis step the reaction mixture was treated at room temperature with deuterium oxide, dideuterated 2-cyclopentenones were readily isolated. As shown in Scheme 2,^[15] the sequential coupling of carbene



Scheme 2. Reactions with other electrophiles.

complex 1g, lithium enolate 2, 1-methoxyallenyllithium (3a) and D₂O provided 5-deuterio-3-deuteriomethyl-2-cyclopentenone **5a** with excellent levels of deuterium incorporation.^[16,17] The deuterium atom in the methyl group at the C3-position of the cyclopentenone ring might indicate the previous presence of a carbon-metal bond at that position, while the deuterium label at the $\alpha'\mbox{-}\mbox{position}$ of the carbonyl group could arise from a hydrogen-deuterium exchange process favoured in the basic medium generated after addition of D₂O at room temperature. Monodeuterated compound 6 was obtained in an experiment in which the source of deuterium was added at low temperature and the saturated aqueous solution of ammonium chloride was added at 0 instead of 20 °C. Thus, the reaction mixture (1 a + 2 + 3 a) generated at $-55 \degree C$ was quenched with deuterated methanol at this same temperature and after 1 h allowing the temperature to raise to 0°C, furnished 3-deuteriomethyl-2cyclopentenone 6 with practically a quantitative isotope incorporation (Scheme 2).^[16] In contrast, the addition at room temperature of ethyl chloroformate to a similar reaction mixture afforded 3-methylenecyclopentene derivative 7 containing a dienol carbonate moiety.

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In the context of the experiments carried out with deuterium oxide we surprisingly found that all at once addition of 5 mL of D_2O instead of 2 mL promoted an instantaneous and complete freezing of the reaction mixture that finally led to the selective formation of a structural isomer of enones **4**. The initial result is shown in Table 2,^[15] entry 1. This reaction mix-



ing) and then -55 to 0°C, 1 h. [b] Yield of isolated, analytically pure product based on carbene complex 1. [c] This initial experiment was carried out twice over to check on the result. [d] In this experiment the reaction temperature after the addition of D₂O was allowed to raise from -55 to 20°C for 3 h and then 20°C, 2 h. [e] In this experiment the reaction mixture formed after the addition of **3a** was stirred at -78°C for 12 h and D₂O was also added at -78°C. [f] In this reaction, H₂O (5 mL) was added instead of D₂O. [g] TBS=*tert*-butyldimethylsilyl. [h] In this experiment DCI (1 m in Et₂O) was added at 20°C instead of NH₄Cl/H₂O at 0°C.

ture was formed by combination of chromium complex 1 a, lithium enolate 2 and allenyllithium 3a and was treated at -55 °C with an excess of D₂O (5 mL). A total solidification of the dark-brown reaction bulk immediately occurred. Keeping the solid mixture for 1 h while the temperature was raised to 0°C did not cause any appreciable change in their physical appearance. The subsequent addition of NH₄Cl/H₂O allowing the mixture to warm to room temperature gave rise to a homogeneous brown solution. The final workup delivered 2,5-dimethoxy-2-cyclohexenone 8a, isolated as a single regioisomer that does not contain any deuterium atom in its structure. To explore the generality of this unexpected process we conducted additional experiments with different aryl- or heteroarylcarbene complexes of chromium 1b,g-k that likewise furnished 2-cyclohexenones 8b-g (Table 2, entries 2-8). Non-deuterated cyclohexenone 8d was also isolated when the solid mixture was permitted to warm to room temperature. After stirring for 2 h at 20°C, the reaction mixture became a brown solution (entry 4). The addition of D_2O at -78 °C to a reaction mixture stirred overnight at -78°C provided an identical result, formation of cyclohexenone 8e (entry 5). This same enone 8e was

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isolated when the solidification of the reaction mixture was accomplished with H₂O in place of D₂O (entry 6). Although the previous experimental procedure to obtain cyclohexenones **8** includes treatment with a big excess of D₂O, incorporation of deuterium was never observed. To get 3-deuterio-2-cyclohexenone **9**^[16] it was necessary to treat the reaction mixture at 20 °C with an ethereal solution of deuterium chloride as indicated in Table 2, entry 9.

Further experiments were conducted to shed some light on this novel modification of the reactivity of an organometallic intermediate by solidification of the reaction mixture with water at low temperature.^[15] First, the reaction of carbene complex **1 a** with lithium enolate **2** and then with allenyllithium **3c** was performed following the standard protocol, but the whole reaction mass was not frozen after addition of the same amount of D₂O (a minor part of the reaction mixture remained liquid). Accordingly, this experiment led to a mixture of cyclohexenone **8h** (major product) and cyclopentenone **4h** (minor isomer) that were easily separated by column chromatography (Scheme 3). In another experiment the solidification



Scheme 3. Formation of compounds $8\,h$ and $4\,h$ under partial freezing conditions.

of the entire reaction mixture was promoted by addition of 1.4-dioxane, under otherwise identical reaction conditions. However, this reaction conducted with 1a, 2 and 3a yielded the corresponding 2-cyclopentenone 4a.[13b,c] Therefore, the use of water to achieve freezing seems to be playing a critical role besides the "physical" solidification of the reaction medium. In a final experiment a reaction mixture formed by sequential combination of 1 a, 2 and 3 a was allowed to warm to room temperature before addition of D_2O (5 mL at -55 °C) that induced full freezing of the mixture.^[13b] This reaction mixture was treated with a saturated aqueous solution of NH₄Cl at 0°C and afforded selectively 3-deuteriomethylcyclopentenone 6 with a roughly complete deuterium labelling.^[16] This result clearly shows that the reaction intermediate generated at low temperature (-55°C) and that formed at room temperature are of different nature.

The structures of products **4–9** were ascertained by 1D and 2D NMR spectroscopy^[18] and subsequently confirmed by two single-crystal X-ray diffraction analyses of compounds **5**a and **11**.^[19,20]

The ring core of cyclopentenones **4** and cyclohexenones **8** have been assembled by joining the carbene ligand (1C unit), the enolate framework (2C unit) and the alkoxyallenyllithium either as a two- or three-carbon synthon through a formal

 $[2_A + 2_E + 1_c]$ or $[3_A + 2_E + 1_c]$ cyclization process, respectively.^[21] On this basis and according to our previous results,^[3-5] we propose the mechanism shown in Scheme 4 to account for the formation of compounds **4–9**. The sequential coupling of the



Scheme 4. Mechanistic pathway for the formation of compounds 4-9.

three starting materials occurs at -78°C by initial nucleophilic addition of amide enolate 2 to the carbene carbon atom of complex 1 to give carbamoyl functionalized alkylchromate intermediate A,^[22] and subsequent nucleophilic addition of allenyllithium reagent 3 to the amide carbonyl group of complex A to form a new lithium alkylpentacarbonylchromate complex B containing two contiguous C-C double bonds at the 4-position with respect to the C–Cr σ bond.^[23] Upon rising the temperature to -55°C adduct B undergoes ring closure as a consequence of the intramolecular insertion of the allene group into the C–Cr σ bond (5-exo-dig cyclization).^[24] Electronic factors govern the regioselective formation of the C-C bond with the central allene carbon atom generating the most stable σ -allylic/ π -allylic chromate complex **C**.^[4, 25] Trapping this intermediate C with MeOD at -55 °C provides after hydrolysis monodeuterated cyclopentenone 6, whereas heating to room temperature promotes a vinylogous β -elimination reaction resulting in the formation of lithium dienolate D. The final reaction of this bidentate nucleophile **D** with H₂O, D₂O or ClCO₂Et provides compounds 4, 5 and 7 depending on the nature of the electrophile. On the other hand, when the reaction mixture generated either at -78 or -55 °C was totally frozen by addition of water (D₂O or H₂O), 4,5-hexadienylchromate complex **B** undergoes a regioselective 6-endo-dig intramolecular carbometalation of the allene fragment furnishing alkenylchromate complex E after reaching room temperature. Presumably, the highly heteroatom-substituted intermediate B interacts with the water molecules forming a hydrogen-bonding network. It is likely

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that this new supramolecular organization joined to the solid state of the reaction mixture are changing the conformation of this intermediate ("solution" conformation **B**' to "frozen" conformation **F**)^[24] sufficiently to reverse the regiochemistry of the ring closure (C–C bond formation at the terminal allene carbon atom). The final hydrolysis or deuterolysis of alkenyl-chromate **E** leads to cyclohexenones **8** and **9**, respectively.

In summary, we have developed a fundamentally novel, efficient and regioselective three-component synthesis of alkoxysubstituted 2-cyclopentenones or 2-cyclohexenones by choosing the appropriate reaction conditions in the cyclization step (anhydrous solution or water-promoted solidification, respectively). Notably, this study has revealed a remarkable and unprecedented water-freezing effect to tune the reactivity of an allenyl-substituted alkylchromate complex that under these solid-state conditions undergoes the intramolecular carbometalation reaction with total reversion of the regioselectivity. In addition, experiments conducted with different electrophiles and under different reaction conditions provided access to deuterated enones and enabled to trap reaction intermediates rendering support for the reaction pathway.^[26]

Experimental Section

Experimental details are provided in the Supporting Information.

Acknowledgements

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Keywords: carbene ligands · cyclization · enones multicomponent reactions · water freezing

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- [15] In these experiments lithium enolate **2** was prepared from *N*-methoxy-*N*-methylacetamide and *t*BuLi (THF, -78 °C, 1 h).
- [16] The percentage of deuterium incorporation was determined from the corresponding quantitative ¹³C NMR spectra (see the Supporting Information).
- [17] In an analogous experiment we have observed that the proportion of deuterium labelling in the Me group at the β -position of the enone moiety was significantly lower when lithium enolate **2** was generated using LDA. Presumably the presence of diisopropylamine provokes some instability of the corresponding metallic intermediate.
- [18] ¹H, ¹³C, DEPT, HSQC, HMBC, COSY and NOESY NMR spectra were measured. 2D NMR spectroscopy was performed on compounds **4a**, **8a** and **8b**.
- [19] Compound 11 was generated from 2-cyclohexenone 8f after removal of the TBS group (product 10 is formed) followed by spontaneous aromatization (see the Supporting Information for details).



[20] CCDC-893312 (5 a) and -893311 (11) 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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- [21] Topological identification of the cyclization reaction (A=allenyl group, E=enolate anion, C=carbene ligand).
- [22] a) This intermediate A has been characterized by 1D and 2D NMR spectroscopy. These results will be reported separately; b) The 1,2-addition reaction of an amide lithium enolate to the carbene carbon atom of a Group 6 Fischer carbene complex is reported for the first time.
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- [26] Further investigations to explore the generality of this water-freezing effect, as well as to better understand the reaction mechanism, are in progress.

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Water-promoted freezing: Three

simple starting materials and a deuteri-

produce isotopically labelled oxygenat-

ed 2-cyclopentenones or 2-cyclohexe-

nones (see scheme). In these multicom-

um source are selectively coupled to



ponent transformations allenyl-substituted alkylchromate complexes undergo a 5-*exo*-dig cyclization when maintained in an anhydrous solution but a 6-*endo*dig cyclization when a water solidified environment is created.

Organic Synthesis

R. De la Campa, J. Flórez*



Water Freezing as a Regiocontrol Element in the Multicomponent Assembly of Cyclic Enones



Water-Freezing Regiocontrol

An efficient modular and regioselective synthesis of deuterated cyclic enones has been achieved by successive coupling of three simple starting materials and a deuterium source. Dialkoxy 2-cyclopentenones were generated under anhydrous conditions, whereas dialkoxy 2-cyclohexenones were formed under water-promoted solidification of the reaction mixture. This unprecedented water-freezing effect induced a total inversion of the regioselectivity in the intramolecular cyclization of allenyl-substituted alkylchromate intermediates. For more details, see the Communication by J. Flórez et al. on page ff.