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1,3-Dipolar Cycloaddition of Hydrazones with α-Oxo-ketenes: A Three-Component Stereoselective Entry to Pyrazolidinones and an Original Class of Spirooxindoles

Marc Presset, Kishor Mohanan, Marie Hamann, Yoann Coquerel,* and Jean Rodriguez*

Institut des Sciences Moléculaires de Marseille (iSm2), Aix-Marseille Université – CNRS, UMR6263, Centre Saint Jérôme, Service 531, 13397 Marseille cedex 20, France

yoann.coquerel@univ-cezanne.fr; jean.rodriguez@univ-cezanne.fr

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ABSTRACT

Stereodefined monocyclic, spirobicyclic, and bis-spirotricyclic pyrazolidin-3-ones can be prepared efficiently by a three-component reaction involving a 1,3-dipolar cycloaddition of azomethine imines obtained from hydrazones with α-oxo-ketene dipolarophiles generated *in situ*. The reaction allows the creation of four covalent bonds and two contiguous chiral quaternary centers with excellent diastereoselectivity in a single catalyst/additive-free, highly atom-economical transformation. From a fundamental point of view, the reaction introduces α-oxo-ketenes as effective dipolarophiles in 1,3-dipolar cycloadditions.

Sequential multiple bond-forming transformations (MBFTs), which include consecutive and domino multicomponent reactions (MCRs), allow the preparation of diverse and sometimes impressively complex molecules in a single chemical operation, thereby largely contributing to the development of sustainable chemistry.[1] They are now firmly established as one of the primary tools of modern organic synthesis and are extensively used in both academic and pharmaceutical company laboratories for the generation of libraries of molecules aiming at the discovery of new therapeutic agents.[2] The invention of new MBFTs, and particularly those involving unprecedented transformations, is of utmost value because they can provide rapid entries to new classes of compounds with unforeseen applications. Herein, we describe a microwave-assisted three-component reaction for the stereoselective preparation of pyrazolidin-3-ones (e.g., **6**) and its application to the synthesis of a new class of spirooxindoles based on an unprecedented reactivity of α-oxo-ketenes.

Pyrazolidin-3-ones are conformationally constrained β-amino acids, some of which exhibit potent antibacterial activities and reducing chemical properties exploited in the industry of photography, and more recently, they have

(1) For efforts to clarify the terminologies of MBFTs, see: (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed.* **1993**, *32*, 131. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (c) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006. (d) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005. (e) Coquerel, Y.; Boddaert, T.; Presset, M.; Mailhol, D.; Rodriguez, J. In *Ideas in Chemistry and Molecular Sciences: Advances in Synthetic Chemistry*; Pignataro, B., Ed.; Wiley-VCH: Weinheim, Germany, 2010; Chapter 9, p 187.

(2) Selected recent reviews: (a) Kruithof, A.; Ruijter, E.; Orru, R. V. A. *Curr. Org. Chem.* **2011**, *15*, 204. (b) Bonne, D.; Coquerel, Y.; Constantieux, T.; Rodriguez, J. *Tetrahedron: Asymmetry* **2010**, *21*, 1085. (c) Jiang, B.; Rajale, T.; Wever, W.; Tu, S.-J.; Li, G. *Chem.—Asian. J.* **2010**, *5*, 2318. (d) Dolle, R. E.; Le Bourdonnec, B.; Worm, K.; Morales, G. A.; Thomas, C. J.; Zhang, W. *J. Comb. Chem.* **2010**, *12*, 765. (e) Estevez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402.

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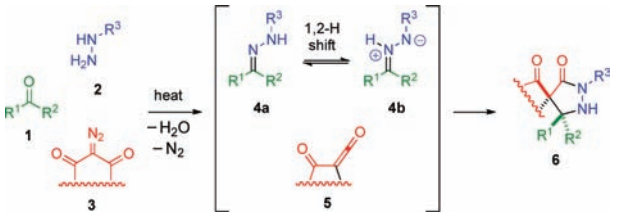
been identified as effective organocatalysts.[3] α-Oxo-ketenes[4] are well-known to react with nucleophiles to produce 1,3-dicarbonyl compounds,[5a] but in sharp contrast with simple ketenes, they almost exclusively react as 1-oxadienes with unsaturations (X=Y or C≡X) in inverse electron demand [4 + 2] oxa-Diels–Alder cycloadditions.[5b] We have recently reported a switch of periselectivity in α-oxo-ketene six-electron cycloadditions, revealing their reactivity as excellent dienophiles in [2 + 4] aza-Diels–Alder cycloadditions with 1-aza-dienes.[5c] Based on this unique reactivity, we surmised that pyrazolidin-3-one **6** could be obtained from the carbonyl compound **1**, the substituted hydrazine **2**, and the diazo compound **3** in a single catalyst-free domino three-component reaction as follows: the rapid formation of hydrazone **4a**, which upon heating should undergo a 1,2-hydrogen shift to give the corresponding azomethine imine 1,3-dipole **4b**,[6] followed by Wolff rearrangement[7] of **3** to **5**, providing the two partners of an original 1,3-dipolar cycloaddition leading to the pyrazolidinone **6** (Scheme 1).

Scheme 1. Planned Synthesis of Pyrazolidin-3-ones



The feasibility of the key 1,3-dipolar cycloaddition relies on the unprecedented behavior of α-oxo-ketenes as efficient dipolarophiles. Besides this, crucial for the success of this synthetic plan is the faster formation of the hydrazone **4a** compared to the α-oxo-ketene **5** to avoid the irreversible nucleophilic addition of hydrazine **2** to **5**. Also, hydrolysis of the α-oxo-ketene **5** with the water produced concomitantly with the formation of the hydrazone **4a** should be avoided. In early experiments, we submitted a 1:1:1 mixture of benzaldehyde, phenylhydrazine, and 5,5-dimethyl-2-diazo-cyclohexan-1,3-dione (diazodimedone) in toluene to microwave irradiation at 140 °C for 15 min (ramp up time = 2 min), and rewardingly, the spiro pyrazolidin-3-one **6a** was obtained in 74% yield as the only detectable regio- and diastereomer (Figure 1). A slightly better yield of **6a** (80%) was obtained when the diazo compound was introduced after 10 min of reaction, and the latter protocol (consecutive reaction) was preferred for this study. The reaction was found very general and accommodates a broad range of each of the three substrates (Figure 1): carbonyl compounds **1** can include aromatic (e.g., in **6a**–**d**), aliphatic (in **6e** and **6f**), and α,β-unsaturated (in **6h**) aldehydes as well as acyclic (in **6i** and **6j**), cyclic (in **6k**–**n**), heterocyclic (in **6o**), and functionalized (in **6j**) ketones; aryl- (e.g., in **6a**), functionalized aryl- (in **6m**), heteroaryl- (in **6g**), alkyl- (e.g., in **6l**), and functionalized alkyl- (in **6d**) hydrazines **2** could be used without noticeable change in efficiency; and finally six- (e.g., in **6a** and **6c**) and seven-membered cyclic (in **6f** and **6n**) and acyclic (in **6b** and **6k**) diazo compounds **3** revealed good precursors of the corresponding α-oxo-ketenes. The structures of spiro pyrazolidinones **6h** and **6i** have been resolved by X-ray diffraction analyses, which confirmed the chemo-, regio- and stereochemical outcome of the reaction.[8] Notably, in most cases the overall transformation allowed the construction of a chiral all-carbon quaternary center[9] adjacent to a second stereocenter with excellent control of the diastereoselectivity. In the case of ketones, the construction of two adjacent quaternary centers resulted in the formation of interesting and challenging structures including bis-spiro scaffolds (in **6l**–**o**). The example of compound **6h** is particularly interesting regarding the periselectivity of 6π electrocyclic processes with α-oxo-ketenes, the 1,3-dipolar cycloaddition mode being preferred to the predictable [4 + 2] and [2 + 4] modes.[10] Our current understanding of the reaction, which accounts for both the observed regio- and diastereoselectivity, invokes a thermodynamically controlled stepwise (or concerted very asynchronous) process via disrotatory 6π electrocyclization of a zwitterionic species as depicted in Scheme 2.[11]

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(4) Reviews: (a) Wentrup, C.; Heilmayer, W.; Kollenz, G. *Synthesis* **1994**, 1219. (b) Kollenz, G.; Ebner, S. In *Science of Synthesis: Houben-Weyl methods of molecular transformations*; Danheiser, R., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 2006; Vol. 23, Chapter 9, p 271. (c) Reber, K. P.; Tilley, S. D.; Sorensen, E. J. *Chem. Soc. Rev.* **2009**, *38*, 3022.

(5) For recent examples from our laboratory, see: (a) Presset, M.; Coquerel, Y.; Rodriguez, J. *J. Org. Chem.* **2009**, *74*, 415. (b) Presset, M.; Coquerel, Y.; Rodriguez, J. *Org. Lett.* **2009**, *11*, 5706. (c) Presset, M.; Coquerel, Y.; Rodriguez, J. *Org. Lett.* **2010**, *12*, 4212.

(6) (a) Grigg, R.; Kemp, J.; Thompson, N. *Tetrahedron Lett.* **1978**, *19*, 2827. (b) Le Fevre, G.; Hamelin, J. *Tetrahedron Lett.* **1978**, *19*, 4503. (c) Arrieta, A.; Carrillo, J. R.; Cossio, F. P.; Díaz-Ortiz, A.; Gómez-Escalonilla, M. J.; de la Hoz, A.; Langa, F.; Moreno, A. *Tetrahedron* **1998**, *54*, 13167.

(7) For an authoritative review, see: Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193.

(8) CCDC 800272 (**6h**), 800274 (**6i**), and 800273 (**10a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the Internet from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif or from the publisher's website at http://pubs.acs.org.

(9) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: Weinheim, Germany, 2005.

(10) For examples of [4 + 2] cycloadditions between α-oxo-ketenes and hydrazono compounds, see: (a) Pulina, N. A.; Zalesov, V. V.; Glebova, E. A. *Chem. Heterocycl. Compd.* **2002**, *38*, 1289. For examples of [2 + 4] cycloadditions of α,β-unsaturated hydrazones, see:(b) Waldner, A. *Helv. Chim. Acta* **1989**, *72*, 1435.

(11) The enthalpies of formation obtained from DFT (B3LYP/6-311G**) calculations (Gaussian) of the three possible products, i.e. the pyrazolidinone **6h**, the oxazinone **A** resulting from a [4 + 2] cycloaddition, and the δ-lactam **B** resulting from a [2 + 4] cycloaddition, are, respectively and relatively to **6h**, 0.0, +10.1, and +6.8 kcal/mol (see Supporting Information for details). A full study on the periselectivity of α-oxo-ketenes cycloadditions is in progress and will be reported in due time.

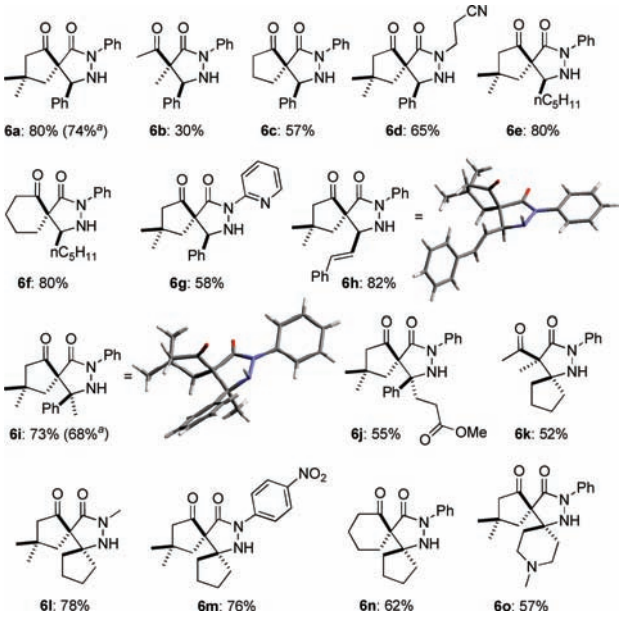
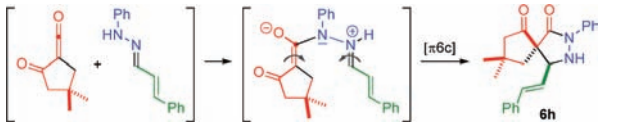


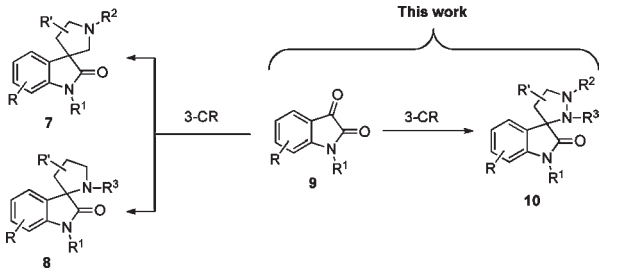
Figure 1. Scope of pyrazolidin-3-ones (dr > 25:1 in all cases). Yields were determined by isolation of the product following silica gel flash chromatography. [a]Yield for the multicomponent protocol; see Supporting Information for details.

Scheme 2. Proposed Pathway



Stimulated by these results, we envisioned the application of the above reaction to the synthesis of an original class of spirooxindoles **10** from isatin derivatives **9** (Scheme 3). Spirooxindoles are privileged heterocyclic molecules generally endowed with biological properties, several of which have recently been identified as useful cellular probes and lead compounds for the development of new therapeutic agents.[12] The most studied and abundant biologically active spirooxindoles are spiro[pyrrolidine-3,3′-oxindoles] of type **7** and the regioisomeric spiro[pyrrolidine-2,3′-oxindoles] of type **8**. Type **7** spirooxindoles are found in many naturally occurring alkaloids biosynthetically derived from tryptamine, while type **8** spirooxindoles are purely synthetic compounds. In both cases, the integration of these compounds in medicinal chemistry and chemical biology research programs has only been made possible by the development of efficient synthetic methods

Scheme 3. Three-Component Strategies toward Spirooxindoles[a]



[a] 3-CR = three-component reaction.

to solve the problem of compound supply and provide a rapid access to collections of molecules.[13] The development of type **7** and **8** spirooxindoles has relied on efficient and versatile domino three-component reactions involving 1,3-dipolar cycloadditions of azomethine ylides with dipolarophiles,[14] which have allowed the preparation of thousands of compounds and the identification of highly potent molecules (Scheme 3).[12,15] From the above analysis, we surmised that spiro[pyrazolidinone-5,3′-oxindoles] of type **10**, which combine both type **7** and **8** spirooxindoles in a single molecule, should be a valuable class of compounds easily assembled by our methodology.[16]

In practice, microwave irradiation at 140 °C of a 1:1:2 mixture of *N*-benzyl isatin, methylhydrazine, and diazodimedone in toluene for 15 min afforded the bis-spirooxindole **10a** as the only detectable diastereomer in 74% yield (Figure 2). As for the previous series, the consecutive reaction protocol was found to be slightly more efficient

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(14) (a) Najera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, *7*, 1105. (b) Eberbach, W. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Padwa, A., Ed.; Georg Thieme Verlag: Stuttgart, 2004; Vol. 27, Chapter 11, p 441.

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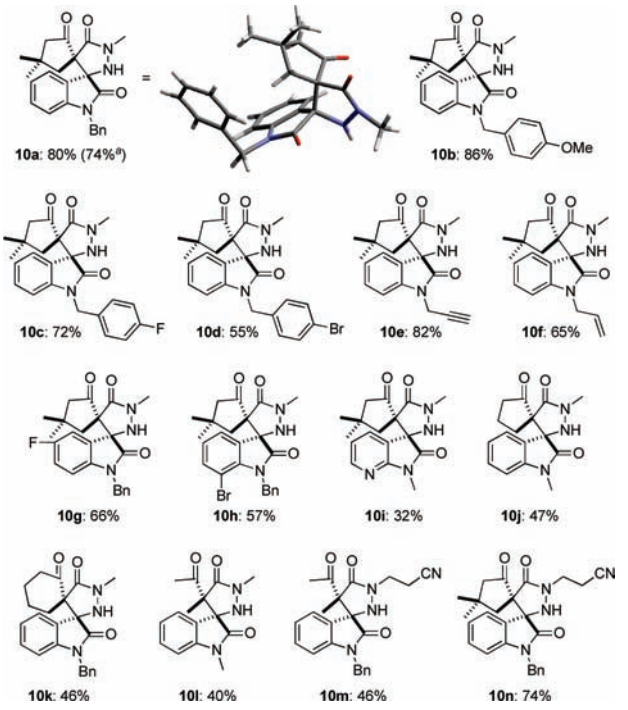

Figure 2. Scope of spiro[pyrazolidinone-5,3′-oxindoles] (dr > 25:1 in all cases). Yields were determined by isolation of the product following silica gel flash chromatography. [a]Yield for the multicomponent protocol; see Supporting Information for details.

and afforded **10a** in 80% yield. The structure of **10a**, which was unambiguously determined by X-ray diffraction techniques,[8] shows an *anti* relationship between the carbonyl groups of the oxindole and the cyclopentanone moieties, and a cage spatial arrangement essentially due to the two contiguous chiral spiro carbon atoms. The scope of the reaction was examined under the optimized conditions, and the results are summarized in Figure 2. In this series, the focus was placed on variations on the oxindole moiety, and a variety of isatin derivatives **9** could be used. Among these several *N*-benzyl- (e.g., in **10a**−**d**), *N*-propargyl- (in **10e**), *N*-allyl- (in **10f**), and *N*-methyl (in **10j** and **10l**) isatin derivatives **9** proved effective; 5-fluoro- and 7-bromo-*N*-benzyl isatin (in **10g** and **10h**, respectively), as well as 7-aza-*N*-methyl-oxindole (in **10i**), were also suitable substrates for the reaction. However, isatin itself (**9**: R = R^1 = H) and *N*-acetyl isatin (**9**: R = H, R^1 = Ac) led to complex mixtures of products. As in the previous series, six- and seven-membered cyclic and acyclic diazo compounds **3** could be used (e.g., in **10i**−**l**). However, in contrast with the previous series, only alkyl- and functionalized alkyl-hydrazines **2** led to the desired spirooxindole **10** (e.g., in **10a** and **10n**, respectively).

Overall, the microwave-assisted three-component (or consecutive, depending on the protocol) reaction described herein introduces α-oxo-ketenes as excellent dipolarophiles in 1,3-dipolar cycloadditions. The reaction has allowed a highly chemo-, regio-, and diastereoselective straightforward synthetic access to a collection of monocyclic, structurally distinct spirobicyclic, and bis-spirotricyclic pyrazolidin-3-ones **6** and **10**, which, based on existing data,[3,12,15] exhibit a certain "drug-like" character. It should be highlighted that the reaction is highly atom-economical, producing only water and nitrogen gas coproducts under additive-free conditions. From a diversity point of view, the reaction intrinsically introduces a ketyl group in position 4 and a free N−H in position 1 on the pyrazolidin-3-one, and its excellent chemoselectivity has allowed the introduction of additional functional groups (cyano, ester, amide, alkene, alkyne, nitro, and halogens for the examples described herein) amenable for further postcondensation reactions. Current work concentrates on the chemistry of type **6** and **10** pyrazolidin-3-ones, their resolution, and the determination of their biological activities.

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Supporting Information Available. Detailed experimental procedures (multicomponent and consecutive reactions); characterization data and copies of ^{1}H and ^{13}C NMR spectra for all compounds; calculation details for **6h**, **A**, and **B**; and CIFs for **6h**, **6i**, and **10a**. This material is available free of charge via the Internet at http://pubs.acs.org.