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Periselectivity Switch of Acylketenes in Cycloadditions with 1-Azadienes: Microwave-Assisted Diastereoselective Domino Three-Component Synthesis of α-Spiro-δ-lactams

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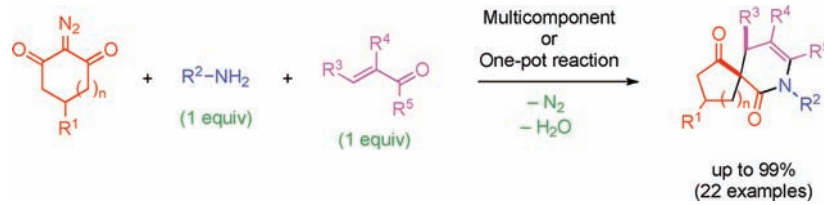
ABSTRACT



The microwave-assisted Wolff rearrangement of cyclic 2-diazo-1,3-diketones in the presence of primary amines and α,β-unsaturated aldehydes provides a straightforward three-component stereoselective access to a variety of α-spiro-δ-lactams following an imination/Wolff rearrangement/[2 + 4] cycloaddition domino sequence. With aniline derivatives, a complementary aza-Wittig/Wolff rearrangement/[2 + 4] sequence was developed. These reactions feature an unprecedented reactivity of acylketenes as dienophiles in 6π electrocyclic processes.

Ketenes[1] are excellent partners in cycloaddition reactions.[2] For example, their [2 + 2] cycloadditions with imines (Staudinger reaction)[3] or alkenes[4] are the most popular routes to β-lactams and cyclobutanones, respectively. Ketenes react preferentially with 1,3-(hetero)dienes to give four-membered rings following [2 + 2] cycloadditions,[5] and there have been only a few examples of ketenes being good dienophiles in [4 + 2] cycloadditions.[6] Both the [2 + 2] and [4 + 2] cycloadditions can take place across either the C=C or the C=O bond of the ketene.[7] In cycloadditions involving acylketenes,[8] the situation is somewhat different. In their s-*Z*

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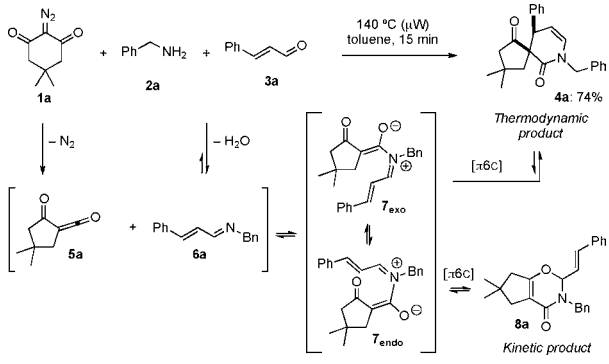
conformation, acylketenes behave almost exclusively as 1,3-oxadienes in inverse demand hetero-Diels−Alder reactions.[9] Examples of [2 + 2] cycloadditions to the ketene function of acylketenes are rare, and with the exception of their cyclodimerization, examples of 6π electrocyclic events involving the C═C bond of acylketenes as dienophiles are unknown.[8] We report herein that under microwave irradiation *in situ* generated 1-azadienes[10] react smoothly with cyclic acylketene dienophiles *via* [2 + 4] cycloaddition to produce diastereoselectively a variety of α-spiro-δ-lactams in a single multiple bond-forming transformation.[11,12]

We recently became interested in applications of the microwave-assisted Wolff rearrangement[13] of 2-diazo-cycloalkan-1,3-diones as a very convenient source of cyclic acylketenes,[14] notably a three-component approach to 1,3-oxazin-4-ones involving the *in situ* formation of the dienophilic C═N double bond.[14b] The projected extension of this methodology to 2-vinyl-1,3-oxazin-4-ones (e.g., **8a**) using α,β-unsaturated aldehydes has revealed an unprecedented periselectivity switch of acylketenes. The microwave irradiation at 140 °C for 15 min of a 1:1:1 mixture of the diazo compound **1a**, benzylamine (**2a**), and cinnamaldehyde (**3a**) unexpectedly furnished the α-spiro-δ-lactam product **4a** as a single diastereomer in 74% yield, resulting from a formal [2 + 4] cycloaddition between the C═C bond of the acylketene **5a** as dienophile and the 1-azadiene **6a** generated *in situ* (Scheme 1). As anticipated, the formation of the

Scheme 1. Periselectivity Switch of Acylketenes in 6π Electrocyclizations



1-azadiene is faster than the formation of the acylketene by Wolff rearrangement under the reaction conditions, thus avoiding the nucleophilic addition of the amine to the acylketene leading to a β-ketoamide product.[14a] According to the stepwise mechanism generally admitted for the Staudinger reaction, the reaction presented in Scheme 1 is believed to involve first the reversible formation of the zwitterionic intermediates $\mathbf{7}_{exo}$ and $\mathbf{7}_{endo}$. The second step, which can be viewed as a reversible six-electron disrotatory electrocyclization, would lead to the spiro compound **4a** from $\mathbf{7}_{exo}$, whereas the oxazinone **8a** would derive from $\mathbf{7}_{endo}$. From these considerations, the periselectivity of the reaction, i.e., [2 + 4] versus [4 + 2] cyclization, would be determined by the relative enthalpies of formation of the two compounds **4a** and **8a**, respectively, with preferential formation of the former.[15] The reversible formation of 2-vinyl-1,3-oxazin-4-ones **8** as depicted in Scheme 1 was unambiguously demonstrated: oxazinone **8j** obtained as a minor byproduct when the reaction of entry 9 (Table 1) is performed at 140 °C (*vide infra*) was converted into the spiro product **4j** (conversion 100%, isolated yield 25%) together with 2-methylcinnamaldehyde (ca. 20%) and degradation after 15 min at 160 °C. A 3,3-sigmatropic rearrangement, which could also account for the conversion of **8j** into **4j**, is not consistent with the observed regeneration of the aldehyde under the reaction conditions.

Spiro compounds are of broad scientific interest due to their unique chemical and conformational features as well as the biological properties often associated with the asymmetric spiro carbon atom. They have attracted considerable attention from the synthetic community.[16] In the case of complex bioactive molecules containing a spiranic subunit, it often occurs that simplified analogues retaining essentially the spiro structural domain exhibit a comparable, and sometimes better, biological profile as the parent compounds.[17] With in mind the application of this new reaction to the synthesis of hitherto unknown small bioactive α-spiro-δ-lactam molecules,[18] we explored its scope and limits.

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(11) For a complementary synthetic approach to α-spirolactams involving a single multiple-bond forming reaction, see: Boddaert, T.; Coquerel, Y.; Rodriguez, J. *Adv. Synth. Catal.* **2009**, *351*, 1744.

(12) For reviews on multicomponent reactions with 1,3-dicarbonyls, see: (a) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957. (b) Liéby-Muller, F.; Simon, C.; Constantieux, T.; Rodriguez, J. *QSAR Comb. Sci.* **2006**, *5*−*6*, 432. (c) Bonne, D.; Coquerel, Y.; Constantieux, T.; Rodriguez, J. *Tetrahedron: Asymmetry* **2010**, *21*, 1085.

(13) Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193.

(14) (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.

(15) The enthalpies of formation obtained from DFT (B3LYP/6-311G**) calculations (Gaussian) showed a preference of 9.9 kcal/mol for the formation of the α-spiro-δ-lactam product **4** over the 2-vinyl-1,3-oxazin-4-one product **8** from methylamine, aldehyde **3a**, and the diazo compound **1c**. A full theoretical study (DFT) of the periselectivities in acylketene cycloadditions is in progress and will be reported in due time.

(16) (a) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007. (b) Pradhan, R.; Patra, M.; Behera, A. K.; Mishra, B. K.; Behera, R. K. *Tetrahedron* **2006**, *62*, 779. (c) Sinibaldi, M.-E.; Canet, I. *Eur. J. Org. Chem.* **2008**, 4391. (d) Raju, B. R.; Saikia, A. K. *Molecules* **2008**, *13*, 1942. (e) Kotha, S.; Deb, A. C.; Lahiri, K.; Manivannan, E. *Synthesis* **2009**, 165.

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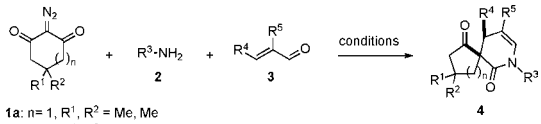
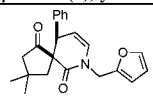
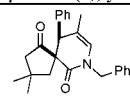
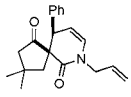
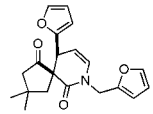
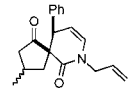
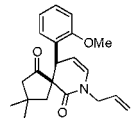
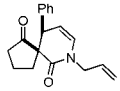
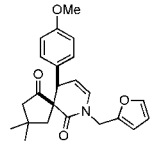
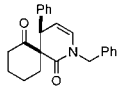
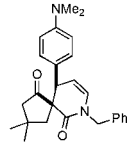
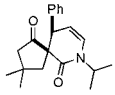
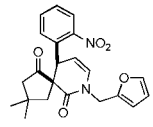
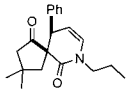
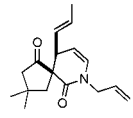
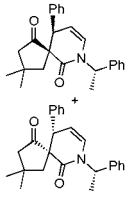
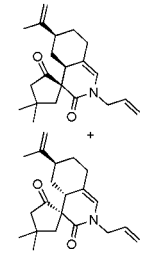
(18) For recent representative examples of de novo biologically active α-spiro-δ-lactams, see: (a) Craig, C. A. (Merck & Co) WO-A1 2010033421, 2010. (b) Selnick, H. G.; Bell, I. M.; Mcwherter, M.; Staas, D. D.; Stachel, S. J.; Steele, T.; Stump, C.; Wood, M. R.; Zartman, C. B. (Merck & Co) WO-A2 2009120652, 2009. (c) Nakagawa, A.; Uno, S.; Makishima, M.; Miyachi, H.; Hashimoto, Y. *Bioorg. Med. Chem.* **2008**, *16*, 7046. (d) Meng, X.; Maggs, J. L.; Pryde, D. C.; Planken, S.; Jenkins, R. E.; Peakman, T. M.; Beaumont, K.; Kohl, C.; Park, B. K.; Stachulski, A. V. *J. Med. Chem.* **2007**, *50*, 6165.

Table 1. Scope and Limits[a]



1a: n= 1, R^1, R^2 = Me, Me
1b: n= 1, R^1, R^2 = Me, H
1c: n= 1, R^1, R^2 = H, H
1d: n= 2, R^1, R^2 = H, H

entry	product(s), yield[b]	entry	product(s), yield[b]
1	 **4b**: 70% (MC), 70% (SW)	9[d]	 **4j**: 74% (SW)
2	 **4c**: 54% (MC), 64% (SW)	10	 **4k**: 52% (SW)
3	 **4d**: 79% (SW), dr = 1.2:1	11	 **4l**: 76% (SW)
4	 **4e**: 73% (SW)	12	 **4m**: 45% (SW)
5[c]	 **4f**: 53% (SW)	13	 **4n**: 50% (MC)
6	 **4g**: 62% (MC), 63% (SW)	14[d,e]	 **4o**: 24% (SW)
7	 **4h**: 50% (MC), 87% (SW)	15[d,e]	 **4p**: 30% (SW)
8	 **4i**: 95% (SW), dr = 1.5:1	16[c]	 **4q**: 47% (SW), dr = 4:1

[a] Unless stated otherwise, all reactions were performed with 1 equiv of each reaction partner in anhydrous toluene (0.4 M) at 140 °C in sealed tubes under microwave irradiation. [b] Yields for isolated product(s) after silica gel flash chromatography. MC refers to the multicomponent protocol, and SW refers to the one-pot stepwise protocol. See Supporting Information for details. [c] Reaction performed at 200 °C. [d] Reaction performed at 160 °C. [e] The formation of the 1-azadiene was incomplete from ^{1}H NMR analysis.

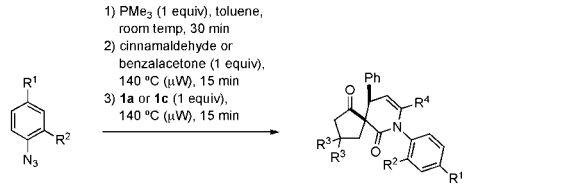
In the above three-component reaction, the *in situ* formation of the 1-azadiene **6a** generates water, which can undergo undesired competitive addition to the acylketene. Thus, during the optimization process, an alternative one-pot stepwise protocol was developed involving first the formation of the 1-azadiene **6a** [from **2a** + **3a** (1:1) in toluene at 140 °C under microwave irradiation for 15 min] and removal of all volatiles under vacuum,[19] followed by addition of the diazo compound **1a** and an additional 15 min of dielectric heating (see Supporting Information for details). Under these optimized one-pot conditions, the spiro compound **4a** could be isolated in 99% yield. The reaction was found to be very general under both conditions (multicomponent or one-pot stepwise), leading to the spiro products **4** from a variety of diazo compounds **1**, primary amines **2**, and α,β-unsaturated aldehydes **3** in fair to high yields (Table 1). In the few cases in which some minor amount of 2-vinyl-1,3-oxazin-4-one **8** was obtained together with the desired spiro compound **4** after 15 min at 140 °C, the reaction temperature was increased to 160−200 °C to give only the spiro product **4** (entries 5, 9, 14−16). The six- and seven-membered diazo compounds **1a**−**d** could be used with comparable efficiencies (entries 2−5). With the chiral acylketene derived from **1b** (entry 3) or an enantiopure primary branched amine (entry 8), a modest chiral induction was observed, but an encouraging diastereoselectivity was obtained in the reaction with (−)-perillaldehyde (entry 16). Of importance, the reaction proved highly chemoselective, and functionalized amines containing a terminal double bond (entries 2−4, 11, 15, and 16) or a 1,3-diene moiety (entries 1, 10, 12, and 14), as well as an aldehyde containing an extra double bond (entry 15) or a 1,3-diene group (entry 10), could be used without production of side products resulting from competitive cycloadditions at these insaturations. These functional groups should prove useful in further postcondensation reactions.

With aniline derivatives, no spiro product was formed under both reaction conditions, possibly because of failures in generating the corresponding imines. This limitation was bypassed by a consecutive aza-Wittig[20]/Wolff rearrangement/[2 + 4] cycloaddition sequence allowing the efficient synthesis of the desired spirolactams **10** bearing an aryl substituent at the nitrogen atom (Scheme 2). The reaction of aryl azides **9** with trimethylphosphine produced the corresponding phosphazenes, which were directly treated with 1 equiv of cinnamaldehyde or benzalacetone in the same reaction vessel and submitted to microwave irradiation to provide the 1-azadienes. To these materials was added the diazo compound, still in the same reactor, and the mixture was submitted again to microwave irradiation to give the expected spiro compounds **10a**−**e** in modest to good yields. The structure of **10c** was confirmed by X-ray diffraction analysis. This consecutive sequence was found nicely complementary to the above-described multicomponent or one-pot reaction,[21] allowing the synthesis of *N*-aryl-substituted products, as well as the introduction of an

(19) In this case, the formation of the 1-azadiene was found quantitative by ^{1}H NMR analysis.

(20) Palacios, F.; Alonso, C.; Aparicio, D.; Rubiales, G.; de los Santos, J. M. *Tetrahedron* **2007**, *63*, 523.

Scheme 2. Consecutive aza-Wittig/Wolff Rearrangement/ [2 + 4] Cycloaddition Sequence



9a: R^1 = OMe, R^2 = H
9b: R^1 = NO_2, R^2 = H
9c: R^1 = Br, R^2 = H
9d: R^1 = H, R^2 = I

10a: R^1 = OMe, R^2 = H, R^3 = R^4 = Me (69%)
10b: R^1 = OMe, R^2 = R^4 = H, R^3 = Me (75%)
10c: R^1 = NO_2, R^2 = R^4 = H, R^3 = Me (35%)
10d: R^1 = Br, R^2 = R^3 = H, R^4 = Me (72%)
10e: R^1 = R^3 = H, R^2 = I, R^4 = Me (21%)

additional alkyl substituant (R^4) on the double bond of the δ-lactam ring when an α,β-unsaturated ketone was used in the aza-Wittig reaction.

In summary, a series of α-spiro-δ-lactams **4** and **10** was prepared efficiently and with high diastereoselectivity by microwave-assisted multiple bond-forming transformations (multicomponent, consecutive, or one-pot reactions) from simple substrates involving an imination (or aza-Wittig)/ Wolff rearrangement/[2 + 4] cycloaddition sequence. These unprecedented transformations, based on the peculiar reactivity of acylketenes as dienophiles in [2 + 4] cycloadditions, nicely combine excellent "economy" (step, atom [waste], raw material, time and energy) with a broad scope of substrates, which makes this approach very attractive for the generation of libraries of synthetically and biologically valuable α-spiro-δ-lactam compounds. From a more fundamental point of view, the herein disclosed reactivity of acylketenes as dienophiles in 6π electrocyclic processes considerably broadens the scope of their chemistry, and was demonstrated to result from a thermodynamic control.

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Supporting Information Available: Experimental procedures and characterization data for all compounds and the crystallographic data for compound **10c** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) For efforts to clarify the terminologies of multiple bond-forming transformations, see: (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed.* **1993**, *32*, 131. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (c) 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, pp 187−202.