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Microwave-Assisted Domino and Multicomponent Reactions with Cyclic Acylketenes: Expeditious Syntheses of Oxazinones and Oxazindiones

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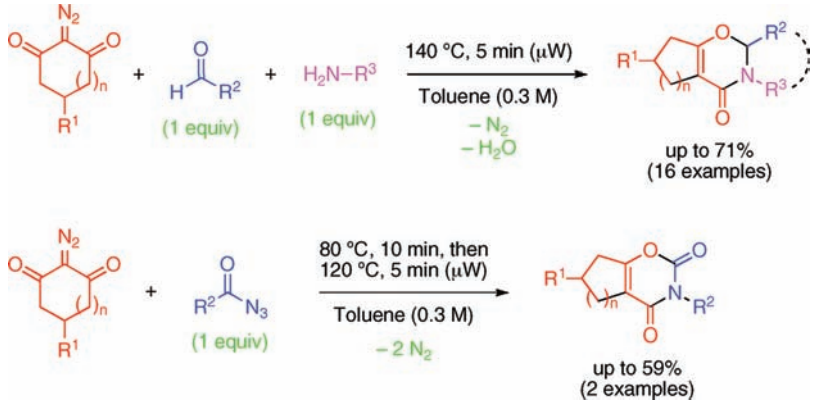
ABSTRACT



The microwave-assisted Wolff rearrangement of cyclic 2-diazo-1,3-diketones in the presence of aldehydes and primary amines provides a straightforward access to functionalized bi- and pentacyclic oxazinones following an unprecedented three-component domino reaction. Alternatively, in the presence of acyl azides, an efficient Curtius/Wolff/hetero-Diels−Alder sequence allows the direct synthesis of oxazindiones.

Contemporaneous research in organic synthesis focuses on economy.[1] Indeed, the efficiency of a synthetic sequence is more than ever corroborated with its conciseness and sustainability issues, as witnessed by the tremendous efforts currently directed at the development of multiple bond-forming[2] and catalytic chemical processes.[3] The efficiency of a chemical synthesis can be measured by parameters such as selectivity and overall yield, of course, but also by its raw material, time, human resources, and energy requirements, as well as the toxicity and hazard of the chemicals and the protocols involved. It is thus now recognized that the step count is one of the most important criteria when evaluating the efficiency of a synthesis. We can note here that the advent of microwave-assisted organic synthesis (MAOS)[4] has contributed significantly to the development of eco-compatible[5] methodologies. In connection with our

(1) Step economy: (a) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40, and references therein. Atom economy: (b) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695, and references therein. Redox economy: (c) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854. For a discussion, using cases-study from complex molecules total syntheses, see: (d) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010.

(2) 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, 2010 and references therein.

(3) Sheldon, R. A.; Arends, I.; Hanefeld, U. *Green Chemistry and Catalysis*; Wiley-VCH: Weinheim, Germany, 2007 and references therein.

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program on the discovery of multiple bond-forming reactions for the synthesis of biologically and/or synthetically relevant coumpounds,[6] we have recently reported a very general and eco-compatible synthesis of α-carbonylated cycloalkanones involving a Wolff rearrangement[7] of cyclic 2-diazo-1,3-diketones followed by trapping of the transient acylketene with nucleophiles in a domino process under microwave irradiation.[8] The synthetic applications of acylketenes are multiple. In the past, they have been largely used for the synthesis of heterocycles, and also for the total synthesis of natural products.[9,10] In their s-*Z* conformation, acylketenes can behave as 1,3-oxadienes in inverse demand hetero Diels−Alder reactions.[9] In particular, their reactions with preformed imines and isocyanates have led to 1,3-oxazin-4-ones and 1,3-oxazine-2,4-diones, respectively. These two closely related classes of compounds can occur in nature and have proven to exhibit some potent biological activities (Figure 1).[11] In this paper, we wish to report our preliminary

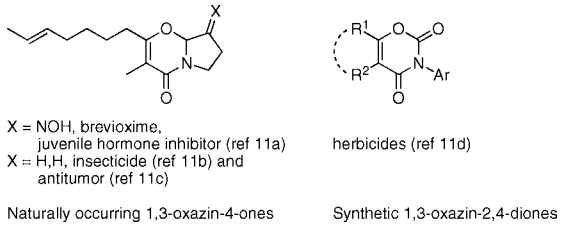
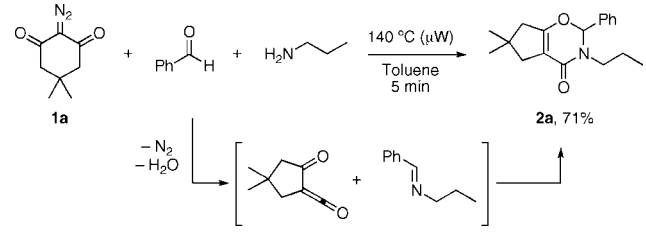


Figure 1. Representative biologically active oxazin(di)ones.

results on the domino and multicomponent microwave-assisted eco-compatible synthesis of 1,3-oxazin-4-ones and 1,3-oxazine-2,4-diones by hetero-Diels−Alder reaction of acylketenes generated by Wolff rearrangement with in situ generated C═N double bonds.

Based on a literature precedent for the catalyst-free microwave-assisted synthesis of aldimines,[12] we surmised that a three-component domino synthesis of oxazinones would be possible by simply irradiating with microwaves a 1:1:1 mixture of a 2-diazo-1,3-diketone, an aldehyde and a primary amine. For the reaction to proceed efficiently, the kinetics of the imine formation should be superior to the kinetics of the acylketene formation by Wolff rearrangement to avoid nucleophilic addition of the amine leading to *β*-ketoamide products.[8] As a test reaction, we submitted an equimolar mixture of the acylketene precursor **1a**, benzaldehyde and *n*-propylamine in toluene to microwave irradiation. Gratefully, after an optimization study, the expected oxazinone **2a** was isolated in 71% yield (Scheme 1).

Scheme 1. Three-Component Domino Synthesis of Oxazinones



Stimulated by this first result we examined the scope and limits of the methodology with various acylketene precursors, aldehydes and amines under the conditions optimized for **2a** (140 °C for 5 min). These results are summarized in Table 1.

The reaction proceeded well with a variety of aromatic (entries 1−6, 10, 11, and 13) and aliphatic (entries 7−9 and 12) aldehydes and with alkyl (entries 1 and 9), allyl (entries 3, 12 and 13), propargyl (entries 4 and 8) and benzyl (entries 2 and 5−7) amines. With enantiopure primary branched amines a modest chiral induction was observed (entries 10 and 11), but no oxazinone products were formed when *tert*-butyl amine and aniline were used, probably due to failures in generating the imine under the reaction conditions. The

(4) For recent monographs or edited volumes on MAOS, see: (a) Kappe, C. O.; Dallinger, D.; Murphree, S. S. *Practical Microwave Synthesis for Organic Chemists: Strategies, Instruments, and Protocols*; Wiley-VCH: Weinheim, Germany, 2009. (b) *Topics in Current Chemistry Vol. 266: Microwave Methods in Organic Synthesis*, Larhed, M.; Olafsson, K., Eds.; Springer, Berlin/Heidelberg, Germany, 2006. (c) *Microwave in Organic Synthesis*, 2nd Edition LoupyA., Ed.; Wiley-VCH, Weinheim, Germany, 2006. For recent representative reviews on MAOS and its applications, see (d) Kappe, C. O. *Chem. Soc. Rev.* **2008**, *37*, 1127. (e) Coquerel, Y.; Rodriguez, J. *Eur. J. Org. Chem.* **2008**, 1125. (f) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563.

(5) We define eco-compatibility as both economical and ecological compatibility.

(6) For selected most recent examples, see: (a) Coquerel, Y.; Filippini, M.-H.; Bensa, D.; Rodriguez, J. *Chem.−Eur. J.* **2008**, *14*, 3078. (b) Reboul, I.; Boddaert, T.; Coquerel, Y.; Rodriguez, J. *Eur. J. Org. Chem.* **2008**, 5379. (c) Boddaert, T.; Coquerel, Y.; Rodriguez, J. *Adv. Synth. Catal.* **2009**, *351*, 1744. (d) Virolleaud, M.-A.; Sridharan, V.; Mailhol, D.; Bonne, D.; Bressy, C.; Chouraqui, G.; Commeiras, L.; Coquerel, Y.; Rodriguez, J. *Tetrahedron* **2009**, *65*, 9756.

(7) For a review, see: (a) Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193. For a recent illustrative example, see: (b) Karpov, G.; Kuzmin, A.; Popik, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 11771.

(8) Presset, M.; Coquerel, Y.; Rodriguez, J. *J. Org. Chem.* **2009**, *74*, 415.

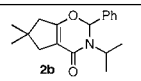
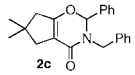
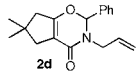
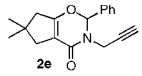
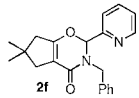
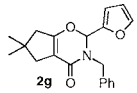
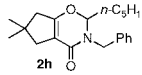
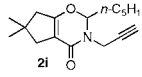
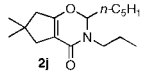
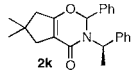
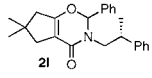
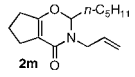
(9) For reviews, see: (a) Wentrup, C.; Heilmayer, W.; Kollenz, G. *Synthesis* **1994**, 1219. (b) Kollenz, G.; Ebner, S. *Science of Synthesis: Houben-Weyl methods of molecular transformations*; Danheiser, R., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 2006; Vol. 23, Chapter 9, pp 271−349. For recent representative examples in the heterocyclic series, see: (c) Pemberton, N.; Jakobsson, L.; Almqvist, F. *Org. Lett.* **2006**, *8*, 935. (d) Pemberton, N.; Pinkner, J. S.; Edvinsson, S.; Hultgren, S. J.; Almqvist, F. *Tetrahedron* **2008**, *64*, 9368. (e) Audouard, C.; Bettaney (née Middleton), K.; Doan, C. T.; Rinaudo, G.; Jervis, P. J.; Percy, J. M. *Org. Biomol. Chem.* **2009**, *7*, 1573 For recent applications in the field of natural product total synthesis, see: (f) Calo, F.; Richardson, J.; Barrett, A. G. M. *Org. Lett.* **2009**, *11*, 4910, and references 7b-f therein. (g) Crimmins, M. T.; Smith, A. C. *Org. Lett.* **2006**, *8*, 1003. (h) Marshall, J. A.; Eidam, P. M. *Org. Lett.* **2008**, *10*, 93. (i) Hoye, T. R.; Danielson, M. E.; May, A. E.; Zhao, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 9743. For a recent review, see: (j) Reber, K. P.; Tilley, S. D.; Sorensen, E. J. *Chem. Soc. Rev.* **2009**, *38*, 3022.

(10) (a) Tidwell, T. T. *Ketenes II*; John Wiley & Sons: Hoboken, NJ, 2006. (b) Tidwell, T. T. *Eur. J. Org. Chem.* **2006**, 563.

(11) (a) Moya, P.; Castillo, M.; Primo-Yúfera, E.; Couillaud, F.; Martinez-Manez, R.; Garcera, M.-D.; Miranda, M. A.; Primo, J.; Martinez-Pardo, R. *J. Org. Chem.* **1997**, *62*, 8544. (b) Cantín, A.; Moya, P.; Castillo, M.-A.; Primo, J.; Miranda, M. A.; Primo-Yúfera, E. *Eur. J. Org. Chem.* **1999**, 221. (c) Nicoletti, R.; Buommino, E.; De Filippis, A.; Lopez-Gresa, M. P.; Manzo, E.; Carella, A.; Petrazzuolo, M.; Tufano, M. A. *World J. Microbiol. Biotechnol.* **2008**, *24*, 189. (d) Doms, P.; Santel, H. J.; Dollinger, M. Eur. Pat. Appl. EP0638563, 1995.

(12) Paquin, L.; Hamelin, J.; Texier-Boullet, F. *Synthesis* **2006**, 1652.

Table 1. Three-Component Domino Synthesis of Oxazinones[a]

entry	diazo	aldehyde	amine	oxazinone	yield
1	**1a**			 **2b**	40%
2	**1a**			 **2c**	54% (61%)[b]
3	**1a**			 **2d**	56% (71%)[b]
4	**1a**			 **2e**	37% (40%)[b]
5	**1a**			 **2f**	53%
6	**1a**			 **2g**	34%
7	**1a**			 **2h**	39%
8	**1a**			 **2i**	35%
9	**1a**			 **2j**	43%
10	**1a**			 **2k**	54%[c]
11	**1a**			 **2l**	47%[d]
12	 **1b**			 **2m**	40%
13	 **1c**			**2n**	36%

[a] All reactions were performed in anhydrous toluene (0.3 M) at 140 °C for 5 min in a sealed tube under microwave irradiation. [b] Reaction performed at 80 °C for 10 min and then 120 °C for 5 min in a sealed tube under microwave irradiation. [c] dr = 2.2:1. [d] dr = 1.3:1.

reaction with the six- and seven-membered ring diazo precursors **1b**,**c** did provide the expected oxazinones **2m**,**n** (entries 12 and 13, respectively), but the less reactive 2-diazo-1,3-cyclopentandione was unproductive even at higher temperature. Of importance, primary amine partners containing a terminal unsaturation could be used successfully, thus allowing for further postcondensations. For example, in the cases where both the aldehyde and amine partners are specifically chosen to participate in a subsequent intramolecular Diels−Alder reaction, we were able to obtain stereoselectively the pentacyclic oxazinone derivatives **3a** and **3b** (Scheme 2). The structure of **3a** was confirmed by

Scheme 2. MCR Domino Synthesis of Pentacyclic Oxazinones

X-ray diffraction analysis.[13] These products are obtained in a multicomponent domino sequence involving four elemental reactions (imine formation, Wolff rearrangement, intermolecular hetero-Diels−Alder, intramolecular Diels−Alder) allowing the stereocontrolled creation of 6 chemical bonds and 4 rings in a single catalyst-free reaction in fair to good yields in regards of the increase of the molecular complexity (an average of 76−82% per bond formed).[14]

At this stage of our study, we wondered if a comparable strategy would be applicable to the synthesis of 1,3-oxazine-2,4-diones.[15] In other words, is it possible to generate an isocyanate capable of a hetero-Diels−Alder cycloaddition with acylketenes under the present conditions of the Wolff rearrangement? One of the most reliable reaction for the preparation of isocyanates is the thermal Curtius rearrangement of acyl azides. Thus, we logically explored if a controlled microwave irradiation of a 1:1 mixture of diazo compound **1a** and the simple acyl azides derived from benzoic and cinnamic acids would allow the preparation of oxazindiones **4a** and **4b**, respectively (Scheme 2).[16] After a brief optimization study, we have indeed found that a gentle dielectric heating could promote the Curtius rearrangement of these acyl azides in the presence of the diazo compound **1a**, which upon elevation of the reaction temperature underwent the Wolff rearrangement to give the corresponding acylketene, which in turn evolved via the expected hetero-Diels−Alder cycloaddition with the in situ generated isocyanate to give the oxazindiones **4a**,**b** (Scheme 3). This

Scheme 3. Domino Synthesis of 1,3-Oxazine-2,4-diones

sequence is a nice illustration of the utilization of dielectric heating for the selective one-pot thermal rearrangements of azido and diazo compounds.

(13) Crystallographic data for the structural analysis have been deposited with The Cambridge Crystallographic Data Centre under the CCDC number 751577 for compound **3a**. These data (CIF) are available as supporting information or can be obtained free of charge from The Cambridge Crystallographic Data Centre via the internet at www.ccdc.cam.ac.uk/data_request/cif.

Overall, two operationally very simple and easily automatizable domino reactions involving acylketenes for the synthesis of 1,3-oxazin-4-ones and 1,3-oxazine-2,4-diones are described. Although the overall yields are typically in the 40−60% range, the simplicity and cleanness of the reactions, combined with the chemical diversity accessible and the rapid increase in the molecular complexity largely make up for what may be regarded as a weakness. It can also be noted that the above approach to 1,3-oxazin-4-ones is the first example of the exploitation of the Wolff rearrangement in a multicomponent reaction. The reactions described herein are expected to facilitate the research and the development of biologically active oxazinones and oxazindiones.

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Supporting Information Available: Experimental procedures, X-ray structural analysis data for **3a**, full analytical data, and copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) As noted by one of the referees, the generation of water during imine formation is a potential hazard to the acylketene intermediate, and may be responsible for the sometimes observed modest overall yield.

(15) For a recent synthesis of 1,3-oxazine-2,4-diones which does not involve an acylketene intermediate, see: Chen, G.; Fu, C.; Ma, S. *Org. Lett.* **2009**, *11*, 2900.

(16) For a conceptually related approach to pyridines from diazo and azido compounds, see: Chen, Z.-B.; Hong, D.; Wang, Y.-G. *J. Org. Chem.* **2009**, *74*, 903.