Organic LETTERS

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Synthesis of 2-Pyridones by Cycloreversion of [2.2.2]- Bicycloalkene Diketopiperazines

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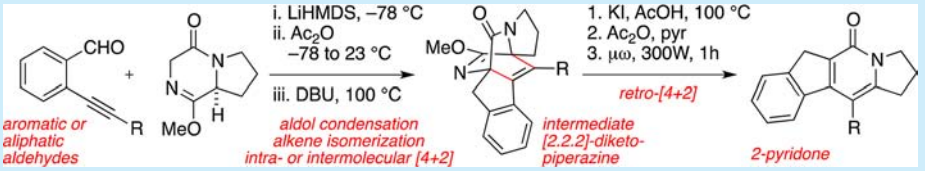
Supporting Information



ABSTRACT: A general strategy for the conversion of [2.2.2]-diazabicyclic alkene structures to 2-pyridone aromatic heterocyclic products is reported. The reaction sequence starts from 2,5-diketopiperazine (DKP) derivatives, is compatible with both aromatic and aliphatic aldehyde components, and can intercept either intra- or intermolecular cycloaddition manifolds. Priming of one aza-bridging function in the intermediate [2.2.2]-DKP scaffold permits cycloreversion (microwave heating) and selective extrusion of cyanate derivatives leading to the formation of 2-pyridone structures. Progress toward the synthesis of louisianin A and B, antiproliferative 2-pyridone natural products, is also disclosed.

2-Pyridones are a valuable and widespread class of aromatic heterocycles. The 2-pyridone scaffold is observed within natural products, pharmaceutical reagents and agrochemicals, and has found applications in polymer[1] and materials chemistry as well as fluorescence imaging.[2] Several biologically active molecules containing this moiety are widely used in the clinic (such as the antitumor agent camptothecin[3] and semisynthetic analogues) or are important lead compounds in the development of new medicinal agents that target cancer, MRSA and VRE bacterial infections, HIV-1, autoimmune disorders, and cognitive decline.[4]

Several means exist for the synthesis of pyridones, but new methods for the preparation (and derivation[5]) of 2-pyridones and 2-alkoxypyridines are relevant and of current interest.[4,6] Although traditional condensation methodologies remain a powerful tool, recently developed strategies centered on metal-catalyzed annulation,[7] olefin metathesis,[8] and novel cyclization chemistry[9] increase the diversity of substituted pyridine and pyridone derivatives that are synthetically accessible. Merged cycloaddition–cycloreversion strategies are known for the synthesis of a number of aromatic heterocycles,[10] although such strategies have been exploited in a limited sense for the synthesis of 2-pyridones.[11] In particular, 5-alkoxy-1,2,4-triazines[12] or 5-silyloxy-1,4-oxazinones[13] will undergo [4 + 2]/retro-[4 + 2] with suitable (electron-rich) dieneophiles.

2-Pyrazinones offer expanded scope and improved reactivity with regard to cycloaddition and readily undergo Diels–Alder reaction with both electron-rich or -deficient dieneophilic substrates at reasonable temperatures, in many cases at or near ambient temperatures.[14,16a] When pyrazinone cycloaddition occurs with alkyne substrates, the resulting [2.2.2]-diazabicyclic adducts can undergo cycloreversion to give 2-pyridones. The original 1970 communication by Porter and Sammes, which demonstrated the first Diels–Alder cycloaddition of a pyrazinone, also noted the thermal decomposition of a [2.2.2]-diazabicyclic alkene cycloadduct (Figure 1).[14a] On

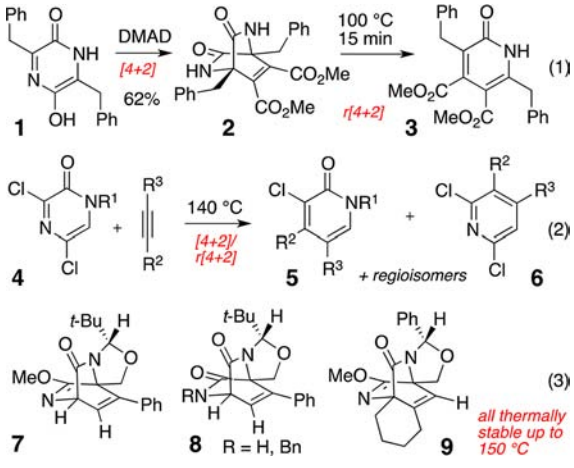


Figure 1. (1,2) Precedent *r*[4 + 2] of [2.2.2]-diazabicycloalkene to 2-pyridone products; (3) thermally stable [2.2.2]-DKP structures.

heating, the diketopiperazine (DKP) cycloadduct **2** underwent cycloreversion and extrusion of isocyanic acid to provide 2-pyridone **3** (yield not given). Other examples of this chemistry are encompassed by adducts derived from cycloaddition of 3,5-dichloro-2(1*H*)-pyrazinone (**4**) (and related derivatives thereof).[15] The aza-bridging functionalities in the intermediate [2.2.2]-cycloadducts derived from 3,5-dichloro-2-pyrazinone

Received: December 18, 2013
Published: January 29, 2014

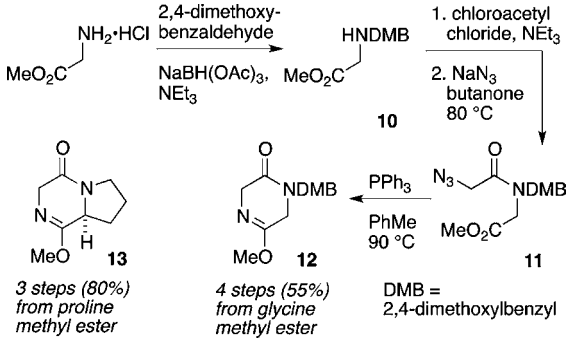
   dx.doi.org/10.1021/ol403632t | *Org. Lett.* 2014, 16, 904–907

substrates are not identical, and cycloreversion affords mixtures of 2-pyridone and pyridine products (**5** or **6**). The predictive capacity of which competing cycloreversion will dominate is limiting, and separation of the mixture of products is not possible in some cases.[15] Because retrograde Diels–Alder reactions that extrude cyanate and cyanogen derivatives are not well understood in comparison to other 2π components[10] (e.g., N_2, CO_2), investigation in this area might provide new insights and increase the synthetic utility of this reaction.

We recently developed a "one-pot" domino reaction sequence comprising an aldol condensation, alkene isomerization, and Diels–Alder cycloaddition for the asymmetric construction of [2.2.2]-diazabicyclic alkaloid structures. In these studies, we employed mostly alkene substrates, but several alkyne dieneophiles were used leading to bicyclo-DKP alkene products (e.g., **7**–**9**).[16] Neither the lactim *O*-methyl ether in **7** or **9** nor the primary or secondary lactam in **8** showed proclivity toward retrograde Diels–Alder reaction; all were thermally stable.

We were curious about the divergent reactivity and threshold for cycloreversion with the Sammes example (eq 1) and with substrates prepared in our lab (eq 3). We set out to explore these differences and targeted two goals: (1) improve the scope and generality of the domino reaction sequence for the construction of [2.2.2]-diazabicyclic DKP structures and (2) determine general conditions for cycloreversion that *selectively* afford 2-pyridone products. While the DKP products (**7**–**9**) bearing the chiral aminal are effective for controlling diastereofacial selectivity in the cycloaddition event, these nonracemic substrates were unnecessary for a methodological study given the achiral nature of the desired 2-pyridone products. Accordingly, we selected two DKP substrates to begin our exploration, the glycine- and proline-derived DKPs **12** and **13** (Scheme 1). The dimethoxybenzyl (DMB)-protected DKP **12**

Scheme 1. Synthesis of DKP Lactim *O*-Methyl Ether Substrates



can be prepared in four operations (55% overall yield). The synthesis of **13** proceeds in analogous fashion (3 steps, 80% yield) from proline methyl ester.[17]

We initiated our study with DKP **13** and 2-ethynylbenzaldehyde (**14a**). Although sodium methoxide is an effective reagent to carry out aldol condensation and alkene isomerization on **13**, the ethynyl benzaldehyde **14a** was not stable and rapidly cyclized to the enol acetal **15** (Scheme 2).[18] By using a non-nucleophilic amide base (LiHMDS) and sequential addition of reagents, the desired reaction sequence could be accomplished. To this end, enolization of the DKP substrate followed by aldol addition into 2-ethynylbenzaldehyde (**14a**) preceded acylation of the intermediate β-alkoxy adduct (Ac_2O, 1.2 equiv). Following exposure to DBU (1.5 equiv), elimination to exocyclic diene **16** and isomerization to **17** was observed and Diels–Alder cycloaddition ensuded, delivering [2.2.2]-DKP adduct **18** in 46% isolated yield. Cycloadduct **18** was thermally stable up to 200 °C.[19] Given the low threshold for extrusion of isocyanate in the Sammes precedent (Figure 1, eq 1), we converted the lactim *O*-methyl ether in **18** to the lactam in **19** (KI, AcOH, 100 °C) in hopes of rendering the cycloreversion more favorable. The resulting DKP **19** was also unreactive toward thermolysis (up to 200 °C).

We then modified the electronic nature of the aza-bridging function in **19** by converting the lactam into the derived lactim carbonate **20**. Thermolysis of **20** (microwave heating, 300 W, 1 h) afforded both the desired cycloreversion product, pyridone **22**, and returned lactam **19**. The presence of lactam **19** as a product indicates that thermal decomposition of the Boc residue is competitive with cycloreversion and extrusion of cyanogen carbonate. Activation of the lactam **19** as the lactim acetate **21** (Ac_2O, pyr) permitted cycloreversion under identical thermolysis conditions but afforded a single observed product, pyridone **22** (84% isolated yield from **19**). In this study, microwave heating emerged as an operationally convenient tool to access elevated temperatures above 150 °C, preserve short reaction durations (1 h), and permit the use of toluene as a reaction solvent (thereby facilitating evaporation following completion of the reaction).

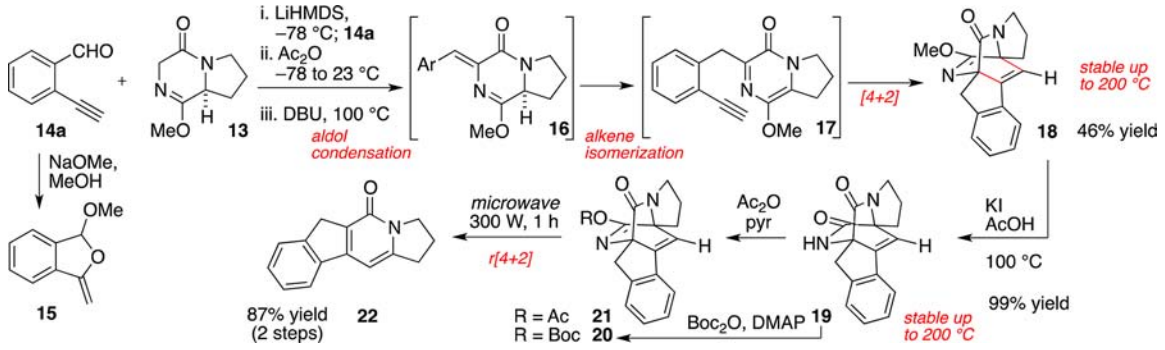
The synthetic sequence leading to pyridones can also be accomplished starting with DKP **13** and benzaldehyde **14b**, which bears aryl substitution at the alkyne terminus (Figure 2). We noted that during thermolysis of the intermediate lactim acetate derived from **24** there was no notable change in the cycloreversion threshold, suggesting that nonbonding interactions do not appreciably accelerate the extrusion of cyanate and formation of pyridone **25**.

The one-pot aldol condensation, alkene isomerization, and Diels–Alder cycloaddition sequence was also completed using the DMB-protected DKP **12** with both **14a** and **14b**. Conversion of corresponding cycloadducts **26a** and **26b** into pyridones **28a** and **28b** proceeded in analogous fashion. The DMB protecting group was retained through the series of reactions leading toward pyridones and proved stable to both demethylation (KI, AcOH, 100 °C) and thermolysis. After becoming inured to frequent use of the microwave, and in order to demonstrate the utility of the DMB as a protecting group for 2-pyridones, we removed the functionality on **28b** with anhydrous acid (TFA in CH_2Cl_2) at 120 °C (15 min, microwave) to reveal the unprotected tricyclic pyridone **29** (78% yield).

In the reactions described thus far, the intermediate [2.2.2]-cycloadducts were prepared by intramolecular Diels–Alder cycloaddition. Intermolecular cycloaddition is also possible but requires slightly modified reaction conditions in order to employ electron-deficient dieneophiles such as dimethylacetylene dicarboxylate (DMAD) (Scheme 3). Toward this end, aldol condensation and alkene isomerization by the usual method (using **13** and benzaldehyde) afforded the intermediate azadiene [4 + 2] precursor **30**. Aqueous workup was required to eliminate residual DBU base (in order to prevent Michael additions) prior to the introduction of DMAD and submission to the Diels–Alder reaction conditions (warming to 60 °C). In this way, the desired [2.2.2]-diazabicyclic cycloadduct **31** could be prepared in 82% yield from **13**.[20]

dx.doi.org/10.1021/ol403632t | *Org. Lett.* 2014, 16, 904–907

Scheme 2. Formation of 2-Pyridone from [2.2.2]-Diazabicyclic Intermediate by Selective Extrusion of Activated Cyanic Acid



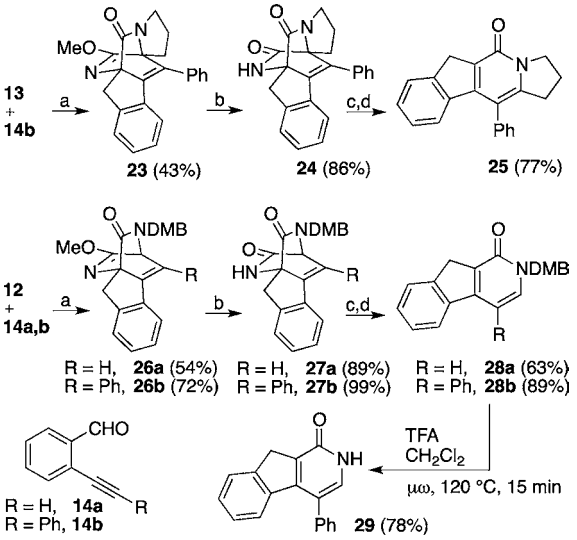
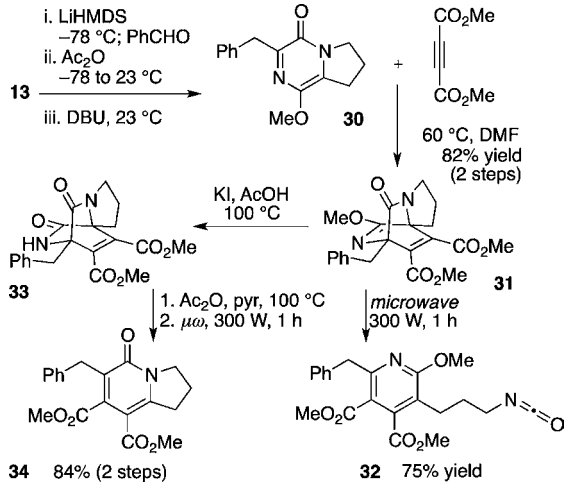


Figure 2. Synthesis of 2-pyridone alkaloids. Standard conditions: (a) (i) LiHMDS, −78 °C; **14a** or **14b**; (ii) Ac_2O, −78 to 23 °C; (iii) DBU, 23 to 100 °C. (b) KI, AcOH, 100 °C. (c) Ac_2O, pyr, 100 °C. (d) Microwave, 300 W, power mode, 1 h.

Scheme 3. Selective Preparation of 2-Pyridone or Regioisomeric 2-Methoxy Pyridine

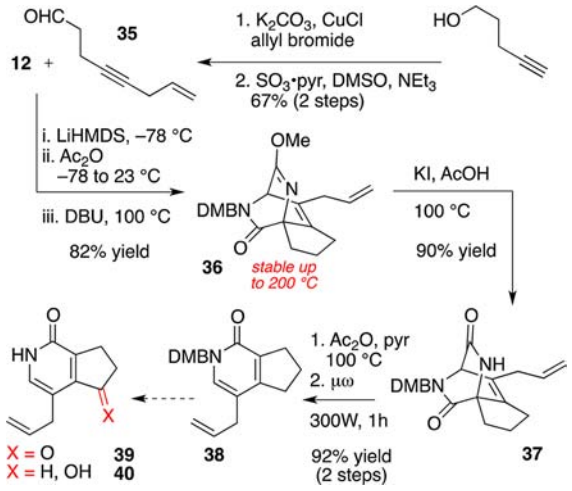


With cycloadduct **31** in hand, we were able to reveal some interesting cycloreversion reactivity. While the standard protocol comprising demethylation, activation, and thermolysis was able to deliver pyridone **34** without event, direct exposure of **31** to thermolysis conditions (300 W, 1 h), promoted the cycloreversion and ejection of the alternate aza bridge (extruded as the tethered isocyanate) to give the observed methoxy pyridine **32** (75% yield).

At this point in the study, we demonstrated a general sequence that can provide 2-pyridones from DKP and aromatic aldehyde components via an intermediate [2.2.2]-diazabicycloalkene cycloadduct. We wanted to also determine if the sequence was viable with aliphatic aldehydes, and we selected louisianin A (**39**) and B (**40**) as as instructive models to validate this chemistry. The louisianin alkaloids possess antitumor activity and were isolated in 1995 from cultured *Streptomyces* sp. WK-4028 found in a Louisiana soil sample.[21] Four distinct strategies toward the louisianin alkaloids have appeared,[22] and two syntheses of **39** are reported.[23]

Our route began with the union of DKP **12** and acetylenic aldehyde **35** using the one-pot reaction sequence to deliver cycloadduct **36** in 82% yield (Scheme 4). The [2.2.2]-

Scheme 4. Synthesis of Louisianin Alkaloids A and B



diazabicycle **36** proved thermally stable up to 200 °C; however, modulating the electronic nature of the lactim bridge again improved the propensity for cycloreversion. Conversion of the lactim *O*-methyl ether in **36** into the lactim acetate enabled cycloreversion at reasonable temperatures and duration (300 W, 1 h) and afforded pyridone **38** in 82% yield from **36** (3 steps). Pyridone **38** contains the core structure of louisianin A and B (**39**, **40**); oxidation and DMB deprotection remain to complete the synthesis of these natural products.

In conclusion, we have demonstrated a general method for the synthesis of 2-pyridones by cycloreversion of [2.2.2]-

dx.doi.org/10.1021/ol403632t | *Org. Lett.* 2014, 16, 904−907

diazabicycloalkene DKP intermediates. Reliable cycloreversion can be accomplished by activation of one aza-bridging functionality as the derived lactim acetate. The synthetic sequence highlights a valuable synthetic route toward 2-pyridones and demonstrates rapid assembly of polycyclic architectures from simple starting materials.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Donors of the ACS Petroleum Research Fund.

■ REFERENCES

(1) Raje, V. P.; Bhat, R. P.; Samant, S. D. *Synlett* **2006**, 2676−2678.

(2) Sellstedt, M.; Nyberg, A.; Rosenbaum, E.; Engstrom, P.; Wickstrom, M.; Gullbo, J.; Bergstrom, S.; Johansson, L. B. A.; Almqvist, F. *Eur. J. Org. Chem.* **2010**, 6171−6178.

(3) (a) Wall, M. E. *Med. Res. Rev.* **1998**, *18*, 299−314. (b) Pommier, Y. *Nat. Rev. Cancer* **2006**, *6*, 789−802.

(4) (a) Torres, M.; Gil, S.; Parra, M. *Curr. Org. Chem.* **2005**, *9*, 1757−1779. (b) Jessen, H. J.; Gademann, K. *Nat. Prod. Rep.* **2010**, *27*, 1168−1185. (c) Mitscher, L. A. *Chem. Rev.* **2005**, *105*, 559−592. (d) Tun, M. K. M.; Herzon, S. B. *J. Exp. Pharm.* **2005**, *4*, 113−123. (e) Haga, A.; Tamoto, H.; Ishino, M.; Kimura, E.; Sugita, T.; Kinoshita, K.; Takahashi, K.; Shiro, M.; Koyama, K. *J. Nat. Prod.* **2013**, *76*, 750−754.

(5) Bisai, V.; Sarpong, R. *Org. Lett.* **2010**, *12*, 2551−2553.

(6) Reviews on the synthesis of pyridones: (a) *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Amsterdam, 2008; Vol. *7*, Chapters 1−6, pp 1−336. (b) Hill, M. D. *Chem.—Eur. J.* **2010**, *16*, 12052−12062. (c) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043−6061. (d) Tieckelmann, H. *Pyridinols and Pyridones in Heterocyclic Compounds*; Abranovitch, R. A., Ed; Wiley: NewYork, 1974; Vol. *14*, pp 597−1180. (e) Varela, J. A.; Saa, C. *Chem. Rev.* **2003**, *103*, 3787−3801. (f) Heravi, M. M.; Hamidi, H. *J. Iran. Chem. Soc.* **2013**, *10*, 265−273.

(7) (a) Hyster, T. K.; Rovis, T. *Chem. Sci.* **2011**, *2*, 1606−1610. (b) Hyster, T. K.; Rovis, T. *Chem. Commun.* **2011**, *47*, 11846−11848. (c) Oberg, K. M.; Lee, E. E.; Rovis, T. *Tetrahedron* **2009**, *65*, 5056−5061. (d) Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2782−2783.

(8) (a) Donohoe, T. J.; Bower, J. F.; Chan, L. K. M. *Org. Biomol. Chem.* **2012**, *10*, 1322−1328. (b) Donohoe, T. J.; Bower, J. F.; Baker, D. B.; Basutto, J. A.; Chan, L. K. M.; Gallagher, P. *Chem. Commun.* **2011**, *47*, 10611−10613. (c) Donohoe, T. J.; Bower, J. F.; Basutto, J. A.; Fishlock, L. P.; Procopiou, P. A.; Callens, C. K. A. *Tetrahedron* **2009**, *65*, 8969−8980. (d) Donohoe, T. J.; Fishlock, L. P.; Procopiou, P. A. *Org. Lett.* **2008**, *10*, 285−288. (e) Donohoe, T. J.; Fishlock, L. P.; Procopiou, P. A. *Chem.—Eur. J.* **2008**, *14*, 5716−5726.

(9) (a) Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007**, *129*, 10096−10097. (b) Parthasarathy, K.; Jeganmohan, M.; Cheng, C. H. *Org. Lett.* **2008**, *10*, 325−328. (c) Pemberton, N.; Jakobsson, L.; Almqvist, F. *Org. Lett.* **2006**, *8*, 935−938. (d) Yavari, I.; Bayat, M. J. *Tetrahedron Lett.* **2011**, *52*, 6649−6651. (e) Rizk, T.; Bilodeau, E. J. F.; Beauchemin, A. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8325−8327. (f) DeKorver, K. A.; Li, H. Y.; Lohse, A. G.; Hayashi, R.; Lu, Z. J.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064−5106.

(10) (a) Rickborn, B. The Retro-Diels−Alder Reaction. Part I. C−C Dienophiles. *Org. React.* **1998**, *52*, 1−393. (b) Rickborn, B. The Retro-Diels−Alder Reaction. Part II. Dienophiles with One or More Heteroatom. *Org. React.* **1998**, *53*, 223−630. (c) Ichihara, A. *Synthesis* **1987**, 207−222. (d) Stajer, G.; Csende, F.; Fulop, F. *Curr. Org. Chem.* **2003**, *7*, 1423−1432. (e) Kotha, S.; Banerjee, S. *RSC Adv.* **2013**, *3*, 7642−7666. (f) Barluenga, J.; Ferrero, M.; Pelaezarango, E.; Lopezortiz, F.; Palacios, F. *J. Chem. Soc., Chem. Commun.* **1994**, 865−866. (g) Igarashi, M.; Nakano, Y.; Takezawa, K.; Watanabe, T.; Sato, S. *Synthesis* **1987**, 68−70.

(11) (a) Gotthardt, H.; Blum, J. *Chem. Ber.* **1987**, *120*, 109−114. (b) Gotthardt, H.; Blum, J. *Chem. Ber.* **1987**, *120*, 115−117. (c) Gotthardt, H.; Blum, J.; Schenk, K.-H. *Chem. Ber.* **1986**, *119*, 1315−1330. (d) Kappe, T.; Pocivalnik, D. *Heterocycles* **1983**, *20*, 1367−1371. (e) Li, G.; Duong, H. M.; Zhang, Z. H.; Xiao, J. C.; Liu, L.; Zhao, Y. L.; Zhang, H.; Huo, F. W.; Li, S. Z.; Ma, J.; Wudl, F.; Zhang, Q. C. *Chem. Commun.* **2012**, *48*, 5974−5976.

(12) Hundsdorf, T.; Neunhoeffer, H. *Synthesis* **2001**, 1800−1805.

(13) Shiori, T.; Takaoka, K.; Aoyama, T. *J. Heterocycl. Chem.* **1999**, *36*, 1555−1563.

(14) (a) Porter, A. E. A.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1970**, 1103. (b) Miller, K. A.; Williams, R. M. *Chem. Soc. Rev.* **2009**, *38*, 3160−3174.

(15) (a) Tutonda, M.; Vanderzande, D.; Vekemans, J.; Toppet, S.; Hoornaert, G. *Tetrahedron Lett.* **1986**, *27*, 2509−2512. (b) Tutonda, M.; Vanderzande, D.; Hendrickx, M.; Hoornaert, G. *Tetrahedron* **1990**, *46*, 5715−5732. (c) Vandenberghe, S. M.; Buysens, K. J.; Meerpoel, L.; Loosen, P. K.; Toppet, S. M.; Hoornaert, G. J. *J. Org. Chem.* **1996**, *61*, 304−308. (d) Buysens, K. J.; Vandenberghe, D. M.; Hoornaert, G. J. *Tetrahedron* **1996**, *52*, 9161−9178.

(16) (a) Morris, E. N.; Nenninger, E. K.; Pike, R. D.; Scheerer, J. R. *Org. Lett.* **2011**, *13*, 4430−4433. (b) Margrey, K. A.; Chinn, A. J.; Laws, S. W.; Pike, R. D.; Scheerer, J. R. *Org. Lett.* **2012**, *14*, 2458−2461.

(17) Laws, S. W.; Scheerer, J. R. *J. Org. Chem.* **2013**, *78*, 2422−2429.

(18) (a) Ito, A.; Kanazawa, C.; Terada, M. *Synlett* **2009**, 638−642. (b) Abbiati, G.; Dell'Acqua, M.; Facoetti, D.; Rossi, E. *Synthesis* **2010**, 2367−2378.

(19) Themolysis of **18** was attempted with both traditional and microwave heating (1,2-dichlorobenzene, 180 °C; 300 W, 1 h, max temp 200 °C).

(20) Precautions were taken to minimize exposure of **30** to air and light. Azadienes such as **30** are fluorescent, and they appear to function as self-sensitizers, producing singlet oxygen (which reacts via cycloaddition with the parent pyrazinone heterocycle). Such reactivity is known, and there is one example of an isolable epidioxydioxopiperazine: Markham, J. L.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1885−1888.

(21) (a) Takamatsu, S.; Kim, Y.-P.; Hayashi, M.; Furuhata, K.; Takayanagi, H.; Komiyama, K.; Woodruff, H. B.; Omura, S. *J. Antibiot.* **1995**, *48*, 1090−1094. (b) Sunazuka, T.; Zhi-Ming, T.; Harigaya, Y.; Takamatsu, S.; Hayashi, M.; Komiyama, K.; Omura, S. *J. Antibiot.* **1997**, *50*, 274−275.

(22) (a) Beierle, J.; Osimboni, E.; Metallinos, C.; Zhao, Y.; Kelly, T. R. *J. Org. Chem.* **2003**, *68*, 4970−4971. (b) Chen, H.; Hsu, R.; Chang, M. *Org. Lett.* **2006**, *8*, 3033−3035.

(23) (a) Chang, C.; Liu, H.; Chow, T. *J. Org. Chem.* **2006**, *71*, 6302−6304. (b) Catozzi, N.; Edwards, M. G.; Raw, S. A.; Wasnaire, P.; Taylor, R. J. K. *J. Org. Chem.* **2009**, *74*, 8343−8354. (c) Catozzi, N.; Wasnaire, P.; Taylor, R. J. K. *Tetrahedron Lett.* **2008**, *49*, 2865−2868.