ORGANIC LETTERS

2007
Vol. 9, No. 20
4057−4060

Efficient Synthesis of Maleimides and Carbazoles via $Zn(OTf)_2$-Catalyzed Tandem Annulations of Isonitriles and Allenic Esters

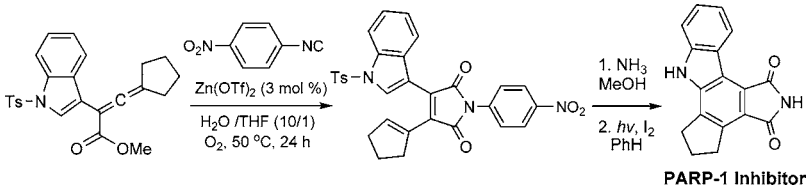
Yuanzhen Li, Haixia Zou, Jianxian Gong, Jing Xiang, Tuoping Luo,[§] Junmin Quan, Guoxin Wang,* and Zhen Yang*

Laboratory of Chemical Genomics, Shenzhen Graduate School, Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education and Beijing National Laboratory for Molecular Science (BNLMS), College of Chemistry and the State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Science, Peking University, Beijing 100871, China

zyang@pku.edu.cn

Received July 27, 2007

ABSTRACT



Lewis acid $Zn(OTf)_2$-catalyzed tandem annulations of isonitriles and allenic esters which lead to efficient and flexible syntheses of a range of biologically significant maleimides and carbazoles and related compounds are reported. A mechanistic rationale is proposed to account for the observed reactivity.

The maleimide and carbazole cores are privileged natural product motifs[1] that are endowed with a wide variety of useful biological activities.[2] Those compounds, both naturally occurring and synthetic, are subjects of intensive investigations in recent years because they serve as important leads in identifying novel molecular identities. For example, pyrrolocarbazole **1** and its analogues are potent PARP-1 [poly(ADP-ribose) polymerase-1] inhibitors;[3] disubstituted maleimide **2** is a highly effective inhibitor of GSK3;[4] and compounds **3** represent a larger group of indolocarbazoles with potent inhibitory effects on MLK1/3 (Figure 1).[5]

Clearly, high-throughput screenings of the biological profiles of these compounds and further studies on their detailed structure−activity relationships with regard to their interactions with protein targets first demand the development of

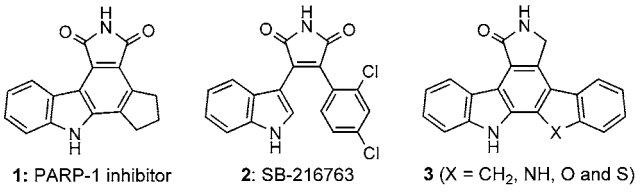


Figure 1. Biologically active maleimides and carbazoles.

[§] Current address: Department of Chemistry and Chemical Biology, Harvard University.

(1) Sánchez, C.; Méndez, C.; Salas, J. A. *Nat. Prod. Rep.* **2006**, *23*, 1007.

(2) (a) Gribble, G. W.; Berthel, S. J. In *Studies in Natural Products Chemistry*; Attaur-Rahman, Ed.; Elesvier Science Publishers: Dordrecht, 1993; Vol. 12. (b) Bailly, C. In *Small Molecule DNA and RNA Binders*; Demeunynck, M., Bailly, C., Wilson, W., Eds.; Wiley-VCH: NY, 2003; Vol. 2, p 538.

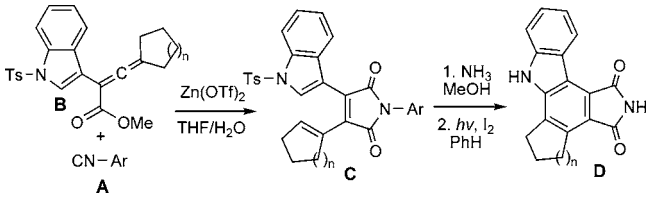
(3) (a) Dunn, D.; Husten, J.; Ator, M. A.; Chatterjee, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 542. (b) Tao, M.; Park, C. H.; Bihovsky, R.; Wells, G. J.; Husten, J.; Ator, M. A.; Hudkins, R. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 938. (c) Wells, G. J.; Bihovsky, R.; Hudkins, R. L.; Ator, M. A.; Husten, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1151. (d) The NMR spectra of our synthesized compound match fully with those provided by Cephalon Inc.

10.1021/ol7018086 CCC: $37.00
Published on Web 08/29/2007

efficient and modular synthetic methods that would allow for the creation of large libraries of these diverse molecular structures.[6] Although many documented synthetic protocols are targeted on the preparation of these pharmaceutically interesting heterocycles,[7] they generally required lengthy steps and lack the modularity that is essential for rapid library construction.

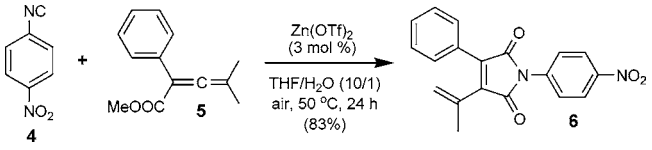
Herein, we report Lewis acid $Zn(OTf)_2$-catalyzed cascade processes[8] initiated from isonitrile[9] **A** and allenic ester[10] **B** that lead to rapid syntheses of substituted maleimides **C** and carbazole derivatives **D** in a sequential manner under mild conditions (Scheme 1).

Scheme 1. $Zn(OTf)_2$-Catalyzed Isonitrile−Allenic Ester Cascade Reaction Leading to Maleimide and Carbazole



The original impetus for this research came from an earlier observation that maleimide **6** could be obtained in 31% yield when isonitrile **4** reacted with allenic ester **5**[11] in THF at 50 °C in the presence of 20 mol % of $Zn(OTf)_2$.[12] We subsequently carried out a systematic optimization and found that the yield of **6** could be eventually improved to 83% by using a mixed solvent of THF and H_2O (10:1) with only a catalytic amount of $Zn(OTf)_2$ (3 mol %) (Scheme 2).

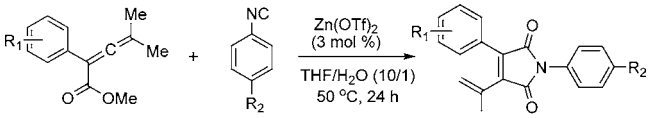
Scheme 2. One-Pot Synthesis of Maleimide **6**

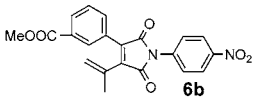
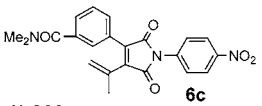
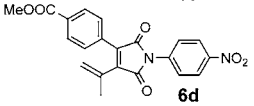
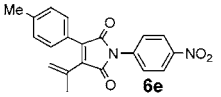
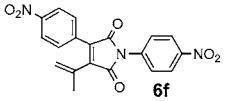
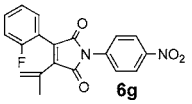


To explore the scope of the above reaction, six additional examples with both electron-withdrawing and electron-donating groups on the phenyl ring were also tested, and delightfully, all yielded analogous products in yields ranging from 56% to 85% (Table 1).

A mechanistic proposal was advanced in Figure 2. We envisaged that isonitrile **E** would act as a nucleophile to attack the central, sp-hybrid carbon of allene **F** activated by the Lewis acidic $Zn(OTf)_2$, and the resultant intermediate **G**

Table 1. Syntheses of Compounds **6b**−**6g**[a]



entry	allene (R_1)	isonitrile (R_2)	product	yield (%)[b]
1	R_1= *m*-COOMe	R_2 = NO_2	 **6b**	56
2	R_1= *m*-$CONMe_2$	R_2 = NO_2	 **6c**	76
3	R_1= *p*-COOMe	R_2 = NO_2	 **6d**	85
4	R_1= *p*-Me	R_2 = NO_2	 **6e**	68
5	R_1= *p*-NO_2	R_2 = NO_2	 **6f**	63
6	R_1= *m*-F	R_2 = NO_2	 **6g**	54

[a] Reagents and conditions: allene (0.6 mmol), isonitrile (0.5 mmol), $Zn(OTf)_2$ (5.5 mg, 0.015 mmol) in THF (8 mL) and H_2O (0.8 mL) at 50 °C for 24 h. [b] Isolated yield.

would then undergo a facile intramolecular cyclization to afford imine **H**. With aromatization as a driving force, **H** could undergo a facile[1,5]-H shift to give furan **I**.[13] Oxidation of the α-position of the furan ring by molecular oxygen[14] and subsequent collapse of the resultant orthoformate **K** in the presence of H_2O would transform **I** into **L**, which finally ring closes to yield the product **M**.[15]

To support the proposed mechanistic sequences, DFT computational modeling was conducted on the step **H** → **I**, and it was found that the [1,5]-H shift was significantly

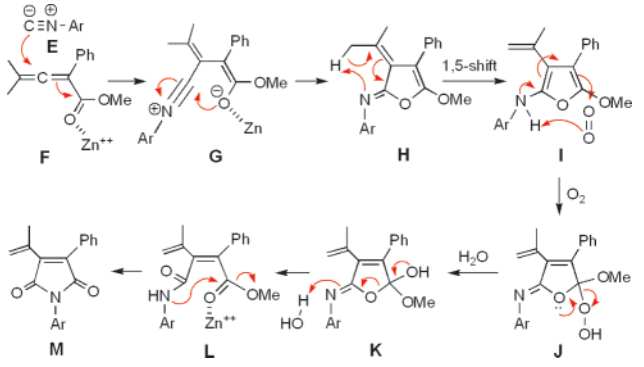


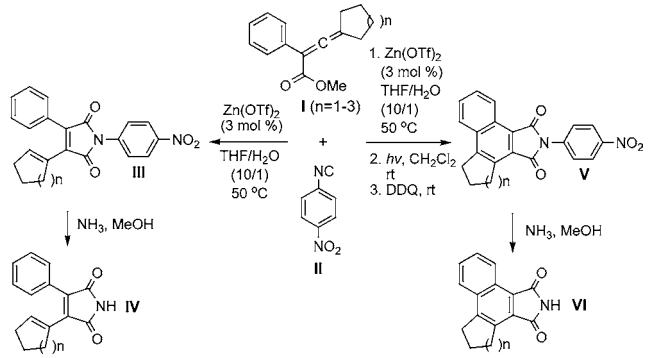
Figure 2. Plausible mechanistic proposal.

(4) Coghlan, M. P.; Culbert, A. A.; Cross, D. A. E.; Corcoran, S. L.; Yates, J. W.; Pearce, N. J.; Rausch, O. L.; Murphy, G. J.; Carter, P. S.; Cox, L. R.; Mills, D.; Brown, M. J.; Halgh, D.; Ward, R. W.; Smith, D. G.; Murray, K. J.; Reith, A. D.; Holder, J. C. *Chem. Biol*. **2000**, *7*, 793.
(5) Hudkins, R. L.; Johnson, N. W.; Angeles, T. S.; Gessner, G. W.; Mallamo, J. P. *J. Med. Chem*. **2007**, *50*, 433.
(6) Hajduk, P. J.; Greer, J. *Nat. Rev. Drug Discovery* **2007**, *6*, 211.

energetically favorable.[16] Furthermore, employment of the d^6-dimethyl deuterated allene substrate led to the corresponding product in which one deuterium was lost from these positions. It merits a note that direct condensation processes of allenes and isonitriles are very rare in the literature.[17] The Lewis acid catalyzed cascades involving these versatile substrates we uncovered here should therefore have useful synthetic and mechanistic implications.

We next directed our attention to delineating the scope and generality of this new synthetic methodology. The facile formation of **6** suggested that our method might be especially useful for making a novel type of cycloalkylaryl-disubstituted maleimide **III**[7i–k] such as structures **C**, which may undergo a direct aminolysis to afford **IV** by treatment of **III** with NH_3 with regard to its easily cleavable 4-nitrophenylamine group. We further envisioned that the formed maleimides **III** should undergo photoinduced in situ 6π-electrocyclic ring closure,[18] followed by oxidative aromatization, to yield products **V**, which could then be readily converted into type-**D** structures **VI** upon aminolysis (Table 2).

Table 2. Syntheses of Compounds **7**−**18**[a]



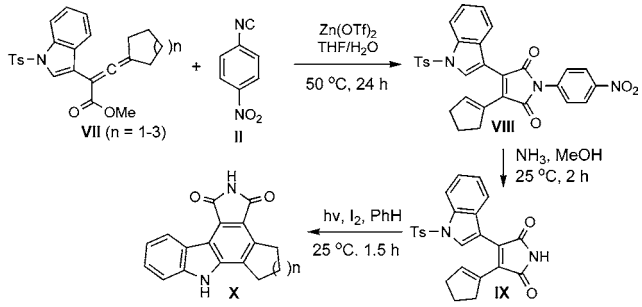
entry	product **III** (yield)[b]	product **IV** (yield)[b]	product **V** (yield)[b]	product **VI** (yield)[b]
1	**7** (60%)	**10** (61%)	**13** (64%)	**16** (73%)
2	**8** (70%)	**11** (70%)	**14** (71%)	**17** (84%)
3	**9**[c] (68%)	**12** (58%)	**15** (46%)	**18** (93%)

[a] Reagents and conditions: see Supporting Information for details on the syntheses of **7**−**18**. [b]Isolated yield. [c]Structure was confirmed by X-ray study.

To that end, allenic esters **I** (n = 1−3) were prepared, and their reactivities under the above-mentioned conditions were examined. To our delight, they all afforded the corresponding products **7**−**12** and **13**−**18** smoothly in good to excellent yields (Table 2), and the structure of **9** was confirmed by X-ray crystallography.

To generate biologically more robust pyrrolo- and indolocarbazoles, indole-fused allenic esters **VII** (n = 1−3) were also made (Table 3) and then subjected to $Zn(OTf)_2$-mediated

Table 3. Syntheses of Compounds **1** and **19**−**26**[a]



entry	product **VIII** (yield)[b]	product **IX** (yield)[b]	product **X** (yield)[b]
1	**19** (56%)	**22** (50%)	**1** (49%)
2	**20** (60%)	**23** (75%)	**25** (71%)
3	**21** (58%)	**24** (79%)	**26** (75%)

[a] Reagents and conditions: (a) allene (0.6 mmol), isonitrile (0.5 mmol), $Zn(OTf)_2$ (5.5 mg, 0.015 mmol) in THF (8 mL) and H_2O (0.8 mL) at 50 °C for 24 h; (b) **VIII** in a saturated solution of NH_3 in MeOH (8 mL) at 25 °C for 2 h; (c) **IX** (0.5 mmol) and I_2 (635 mg, 2.5 mmol) in PhH (100 mL) under $h\nu$ at 25 °C for 1.5 h. [b]Isolated yield.

maleimide formation (**VIII**), aminolysis (**IX**), and photoinduced oxidative 6π-electrocyclization (**X**) to give their corresponding products **19**−**21**, **22**−**24**, **1**, and **25** and **26**,

(7) For selected references, see: (a) Joyce, R. P.; Gainor, J. A.; Weinreb, S. M. *J. Org. Chem.* **1987**, *52*, 1177. (b) Davis, P. D.; Bit, R. A.; Hurst, S. A. *Tetrahedron Lett.* **1990**, *31*, 2353. (c) Davis, P. D.; Hill, C. H.; Lawton, G.; Nixon, J. S.; Wilkinson, S. E.; Hurst, S. A.; Keech, E.; Turner, S. E. *J. Med. Chem.* **1992**, *35*, 177. (d) Porter, B.; Ross, B. C. *J. Org. Chem.* **1992**, *57*, 2105. (e) Wood, J. L.; Stoltz, B. M.; Dietrich, H.-J.; Pflum, D. A.; Petsch, D. T. *J. Am. Chem. Soc.* **1997**, *119*, 9641. (f) Hudkins, P. L.; Johnson, N. W. *J. Heterocycl. Chem.* **2001**, *38*, 591. (g) Trost, B. M.; Krische, M. J.; Berl, V.; Grenzer, E. M. *Org. Lett.* **2002**, *4*, 2005. (h) Kuethe, J. T.; Wong, A.; Davies, I. W. *Org. Lett.* **2003**, *5*, 3721. (i) Stewart, S. G.; Polomska, M. E.; Lee, R. W. *Tetrahedron Lett.* **2007**, *48*, 2241. (j) Wang, J.; Soundarajan, N.; Liu, N.; Zimmermann, K.; Naidu, B. N. *Tetrahedron Lett.* **2005**, *46*, 907. (k) Dubernet, M.; Caubert, V.; Guillard, J.; Viaud-Massuard, M.-C. *Tetrahedron* **2005**, *61*, 4585.

(8) For a recent review on tandem catalysis, see: Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001.

(9) For leading reference, see: Dömling, A. *Chem. Rev.* **2006**, *106*, 17.

(10) For leading reference, see: Ma, S. *Chem. Rev.* **2005**, *105*, 2829.

(11) Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367.

respectively, in good yields, indicating that the methodology is quite general in assembling structurally diverse heterocycles (Table 3). Moreover, the approach provided a concise total synthesis of PARP-1 inhibitor **1** that has an IC_{50} as low as 36 nM.[3]

In an initial effort to investigate kinase inhibition of these synthesized compounds, we set out to profile five representative structures against a panel of kinases covering the entire human kinome.[19]

We have chosen **6e′**, **6b′**, **11**, **12**, and **16** which represent the key scaffolds of the synthesized maleimides. As shown in Figure 3, these five compounds demonstrated distinct

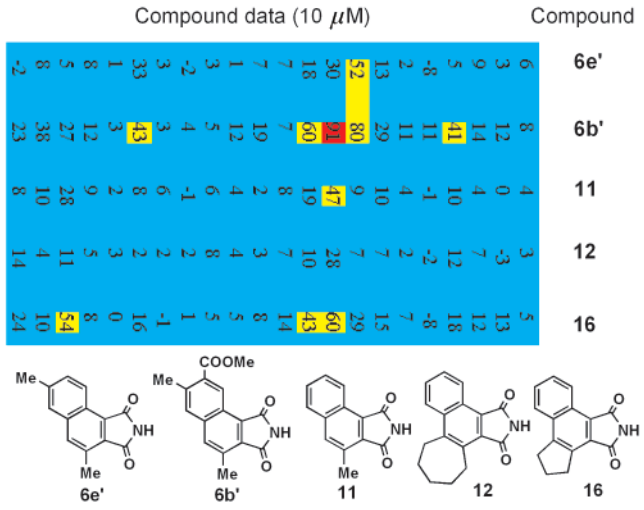


Figure 3. Biological profiles of five representative compounds against a panel of kinases.

inhibition profiles against the panel when tested at the 10 μM level, with compound **12** being weakly responsive, compound **16** being moderately active, and compound **6b′** being the most potent yet less selective. Compounds **6e′** and **11** predominantly hit one kinase, and compound **6b′** inhibits one kinase strongly (at about 90% inhibition) but four other kinases at medium levels. The hitmap compiled in Figure 3 overall suggests that their biological profiles are quite different.

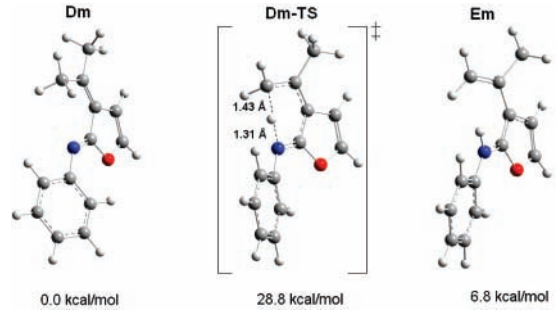
In summary, we have developed Lewis acid $Zn(OTf)_2$-catalyzed tandem annulations of isonitriles and allenic esters that enable efficient and flexible syntheses of a range of structurally interesting and biologically active maleimides and carbazoles and related molecules. The substrates employed in these processes are readily available; the reaction conditions are exceptionally mild; and the generated compounds are amenable for further structural modifications. This method is therefore of considerable value in combinatorial chemistry, diversity-oriented synthesis, drug discovery, and natural products synthesis. Efforts along this line are currently underway in our laboratories.

Acknowledgment. This work was supported by grants from the National Science Foundation of China (20325208, 20225318, 20521202). The kinase selectivity profiling data shown in Figure 3 were kindly provided to us by Pfizer Research Technology Center at Carbridge, MA, U.S.A. We also thank Dr. David Zhigang Wang of Columbia University Chemistry Department for useful discussions.

Supporting Information Available: Experimental, computational (including coordinates), and X-ray structural details. This material is available free of charge via the Internet at http://pubs.acs.org.

OL7018086

(12) Xia, Q.; Ganem, B. *Org. Lett.* **2002**, *4*, 1631.
(13) Nair, V.; Vinod, A. U. *Chem. Commun.* **2000**, 1019.
(14) Ma, S.; Wu, B.; Shi, Z. *J. Org. Chem.* **2004**, *69*, 1429.
(15) An alternative mechanism involving [4+2] cycloaddition of singlet oxygen to furan **I** was ruled out because the operation of this reaction requires neither light nor sensitizer. (For a leading reference, see: Vassilikogiannajis, G.; Margaros, I.; Montagnon, T.; Stratakis, M. *Chem.−Eur. J.* **2005**, *11*, 5899.) Another pathway involving nucleophilic addition of H_2O to a Lewis acid activated furan ring is also unlikely as the use of H_2O^{18} does not lead to the incorporation of the oxygen atom in the product (see Supporting Information for details).
(16) The estimated activation free energy is 28.8 kcal/mol and is much lower than the diene system (see Supporting Information for details).



(17) In one system we were aware of, the reaction terminated at structure **H**: Avetisyan, E. A.; Gambaryan, N. P. *Russ. Chem. Bull.* **1974**, *8*, 1904.
(18) Greshock, T. J.; Funk, R. L. *J. Am. Chem. Soc.* **2006**, *128*, 4946.
(19) The kinase selectivity profiling data were collected at Pfizer Research Technology Center at Carbridge, MA, U.S.A.