ORGANIC LETTERS

2012
Vol. 14, No. 8
2191–2193

The Diels–Alder Cyclization of Ketenimines

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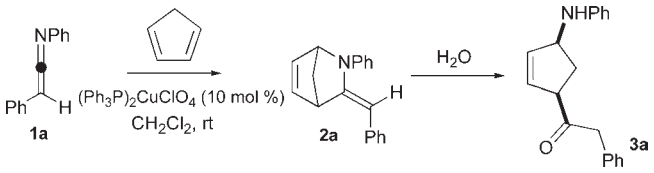
Received March 22, 2012

ABSTRACT



A Diels–Alder reaction between cyclopentadiene and a variety of ketenimines is reported. A copper(I)-bis(phosphine complex catalyzes the cycloaddition across the C=N bond of the ketenimine in a [4 + 2] reaction to give an enamine intermediate that is hydrolyzed upon purification to generate aminoketones.

The Diels–Alder reaction of ketenes and dienes has achieved a mythical status in organic chemistry due to its problematic nature and the unusual mechanistic pathways it follows. For example, ketenes are known to react by parallel [4 + 2] and/or subsequent [2 + 2] manifolds, often in complex ways (Scheme 1).[1] In contrast, keteniminium salts are known to add dienes across their C=C bonds in a [4 + 2] manner.[2] However, the corresponding Diels–Alder reaction involving ketenimines is scarcely known[3,4] in the literature; the basic documentation of such a reaction would provide an important mechanistic counterpoint to the seminal ketene cycloaddition reaction. In this communication, we present a Lewis acid catalyzed Diels–Alder reaction between dienes with ketenimines and elucidate the similarities and differences of this unique reaction to the corresponding process involving ketenes. What is more, this reaction represents a different approach to the catalytic synthesis of enamine intermediates,[5] whose importance to synthetic chemistry grows with each passing year.[6] In contrast to other catalytic enamine syntheses, the amino group is retained in the product, affording potential appeal

(1) For Diels–Alder reactions of ketenes, see: (a) Gonzalez-James, O. M.; Kwan, E. E.; Singleton, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 1914–1917. (b) Allen, A. D.; Tidwell, T. T. *Eur. J. Org. Chem.* **2012**, 1081–1096. (c) Paull, D. H.; Weatherwax, A.; Lectka, T. *Tetrahedron* **2009**, *65*, 6771–6803. (d) Fu, N.; Tidwell, T. T. *Tetrahedron* **2008**, *64*, 10465–10496. (e) Cossio, F. P.; Arrieta, A.; Sierra, M. A. *Acc. Chem. Res.* **2008**, *41*, 925–936. (f) Ussing, B. R.; Hang, C.; Singleton, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 7594–7607. (g) Tidwell, T. *Ketenes II*; John Wiley & Sons: Hoboken, NJ, 2006. (h) Orr, R. K.; Calter, M. A. *Tetrahedron* **2003**, *59*, 3545–3565. (i) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650–1667. (j) Singleton, D. A.; Wang, Y.; Yang, H. W.; Romo, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1572–1575. (k) Tidwell, T. *Acc. Chem. Res.* **1990**, *23*, 273–279.

(2) (a) Ding, P.-Y.; Ghosez, L. *Helv. Chim. Acta* **2005**, *88*, 2022–2031. (b) Ding, W.-J.; Fang, D.-C. *J. Org. Chem.* **2001**, *66*, 6673–6678. (c) Shim, P.-J.; Kim, H.-D. *Tetrahedron Lett.* **1998**, *39*, 9517–9520. (d) Snider, B. B. *Chem. Rev.* **1988**, *88*, 793–811.

(3) While the Diels–Alder reaction of ketenimines is rare, other cycloaddition variants are known for ketenimines, especially those in which they act as four-electron components. For [4 + 2] cycloadditions of ketenimines, see: (a) Navarro-Vázquez, A.; Alonso-Gómez, J.-L.; Lugtenburg, J.; Cid, M.-M. *Tetrahedron* **2010**, *66*, 3855–3860. (b) Alajarin, M.; Bonillo, B.; Marin-Luna, M.; Vidal, A.; Orenes, R.-A. *J. Org. Chem.* **2009**, *74*, 3558–3561. (c) Alajarín, M.; Bonillo, B.; Sánchez-Andrada, P.; Vidal, A.; Bautista, D. *J. Org. Chem.* **2007**, *72*, 5863–5866. (d) Alajarín, M.; Vidal, A.; Ortín, M.-M. *Tetrahedron* **2005**, *61*, 7613–7621. (e) Alajarín, M.; Vidal, A.; Tovar, F.; Sánchez-Andrada, P.; Bautista, D. *Tetrahedron* **2003**, *59*, 9913–9918. (f) Martorell, A.; Inman, G.; Alper, H. *J. Mol. Catal. A: Chem.* **2003**, *204–205*, 91–96. (g) Lee, K.-J.; Kim, D.-W.; Kim, B.-G. *J. Heterocycl. Chem.* **2003**, *40*, 363–367. (h) Alajarín, M.; Vidal, A.; Ortín, M.-M.; Tovar, F. *Synthesis* **2002**, 2393–2398. (i) Alajarín, M.; Vidal, A.; Tovar, F. *Tetrahedron Lett.* **2000**, *41*, 7029–7032. (j) Alajarín, M.; Vidal, A.; Tovar, F.; Conesa, C. *Tetrahedron Lett.* **1999**, *40*, 6127–6130. For [2 + 2] cycloadditions of ketenimines, see: (a) Alajarín, M.; Vidal, A.; Tovar, F.; Ramírez de Arellano, M. C. *Tetrahedron: Asymmetry* **2004**, *15*, 489–494. (b) Alajarín, M.; Vidal, A.; Tovar, F.; Ramírez de Arellano, M. C.; Cossío, F. P.; Arrieta, A.; Lecea, B. *J. Org. Chem.* **2000**, *65*, 7512–7515. (c) Cossío, F. P.; Arrieta, A.; Lecea, B.; Alajarín, M.; Vidal, A.; Tovar, F. *J. Org. Chem.* **2000**, *65*, 3633–3643. (d) Alajarín, M.; Vidal, A.; Tovar, F.; Arrieta, A.; Lecea, B.; Cossío, F. P. *Chem.—Eur. J* **1999**, *5*, 1106–1117. (d) Alajarín, M.; Molina, P.; Vidal, A. *Tetrahedron Lett.* **1996**, *37*, 8945–8948.

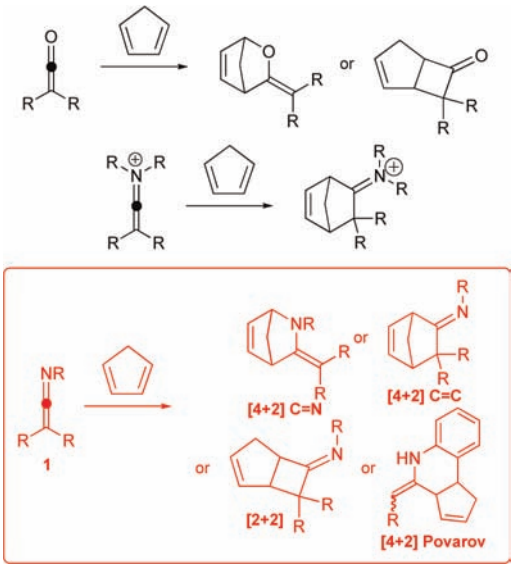
(4) Yavari, I.; Nematpour, M.; Ghazanfarpour-Darjani, M. *Tetrahedron Lett.* **2012**, *53*, 942–943.

(5) (a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569. (b) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discov. Today* **2007**, *12*, 8–27. (c) List, B. *Chem. Commun.* **2006**, 819–824. (d) List, B. *Acc. Chem. Res.* **2004**, *37*, 548–557. (e) Notz, W.; Tanaka, J.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580–591.

10.1021/ol300742t
Published on Web 04/05/2012

for the synthesis of amine building blocks and pharmacologically relevant targets.[7]

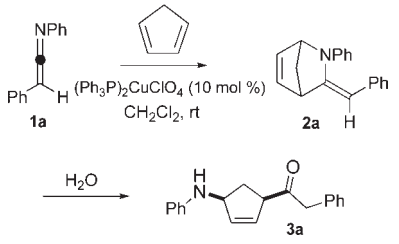
Scheme 1. Diels–Alder Cyclization Pathways



At the beginning of our study, the first question we addressed was in the nature of the products that would form during the reaction of a ketenimine and a diene (Scheme 1). For example, would the reaction follow the ketene precedent and afford the corresponding mixture of enamine or cyclobutanimine products from [4 + 2] and [2 + 2] reactions? Would the iminium salt precedents[2] be followed instead to yield [4 + 2] adducts across the C=C bond? Would the ketenimine operate as an imine and undergo a [4 + 2] Povarov[8] if provided with an *N*-substituted aromatic ring? Or would it follow its own unique variation?

In analogy with the reaction of cyclopentadiene (CpH) and disubstituted ketenes,[1a] we first attempted a reaction of CpH with 1,3,3-trisubstituted ketenimines. Under all conditions, we observed at most trace amounts of cycloadducts. Next we examined potentially more reactive (but much harder to handle) 1,3-disubstituted ketenimines.[9] For example, we first investigated the reaction of 1,3-diphenylketenimine with CpH. We found that the thermal pathway proceeds in a sealed tube under elevated temperatures (180 °C) to afford a modest amount of cycloadduct (20%). At that time, we turned instead to screening potential Lewis acid catalysts for the reaction. We first tried Lewis acids that were previously shown to catalyze the cyclization of dienes with imines,[10] such as $Sc(OTf)_3$, AgOTf, and BF_3•etherate; all of these candidates gave (at most) trace amounts of product, with the notable exception of $(Ph_3P)_2CuClO_4 \cdot (MeCN)_2$,[11] which resulted in **3a** (60% yield) after aqueous workup (Scheme 2). The other possible products listed in Scheme 1 were ruled out based on NMR data, and only **3a** was isolated from each reaction.

Scheme 2. Diels–Alder Cyclization of 1,3-Diphenylketenimine



Rather than an imine or enamine, spectroscopic evidence surprisingly revealed **3a** to be an amino ketone possessing a five-membered ring core. This product would be most likely derived from the hydrolysis of strained enamine **2a** upon workup conditions after the Diels–Alder cyclization had occurred. To examine this possibility, we performed an in situ NMR experiment in order to observe the enamine directly. A standard catalyzed reaction was conducted in $CDCl_3$ and monitored by ^1H and ^{13}C NMR. Two ^1H resonances at δ 4.15 and 4.60 ppm (area 1:2) grew in over time and disappeared upon the introduction of aqueous acid, replacing the vinyl proton of the enamine in monotonic fashion. These peaks, putatively due to the vinyl hydrogens, are consistent with diastereomers of the enamine product. Likewise, two ^{13}C resonances (both enamine isomers) were observed at 102.6 and 101.9 ppm. A calculation[12,13] of the ^{13}C NMR chemical shift of the enamine vinyl carbon (B3LYP/6-311++G**) shows excellent agreement with experiment as well, producing chemical shifts of 101.5 and 100.8 ppm. It is important to note that in contrast to the very complex ketene-diene cycloaddition potential energy surface, Cope rearrangement of the initially formed enamine to the cyclobutanimine does not occur, even at elevated temperatures.

(6) (a) Pihko, P. M.; Majander, I.; Erkkilä, A. *Top. Curr. Chem.* **2010**, *291*, 29–75. (b) Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2008**, *47*, 42–47. (c) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138–6171.

(7) For synthesis of *N*-heterocycles, see: (a) Iwasa, E.; Hamashima, Y.; Sodeoka, M. *Isr. J. Chem.* **2011**, *51*, 420–433. (b) Perreault, S.; Rovis, T. *Chem. Soc. Rev.* **2009**, 3149–3159. (c) Sodeoka, M.; Hamashima, Y. *Pure Appl. Chem.* **2008**, *80*, 763–776. (d) Shimizu, M.; Sodeoka, M. *Org. Lett.* **2007**, *9*, 5231–5234. (e) *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Cordell, G. A., Eds.; Academic: New York, 1992.

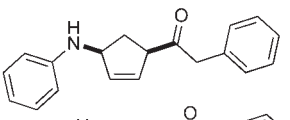
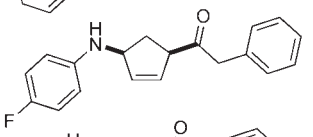
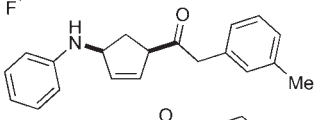
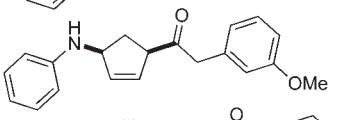
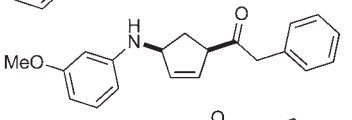
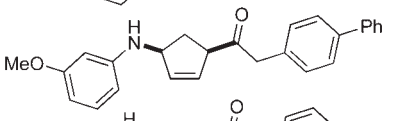
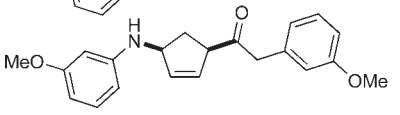
(8) Kouznetsov, V. *Tetrahedron* **2009**, *65*, 2721–2750.

(9) McCarthy, D. G.; Hegarty, A. F *J. Chem. Soc., Perkin Trans. 2* **1980**, 579–591.

(10) (a) Bhargava, G.; Mohan, C.; Mahajan, M. P. *Tetrahedron* **2008**, *64*, 3017–3024. (b) Bhargava, G.; Kumar, V.; Mahajan, M. P. *Tetrahedron Lett.* **2007**, *48*, 2365–2368. (c) Hermitage, S.; Howard, J. A. K.; Jay, D.; Pritchard, R. G.; Probert, M. R.; Whiting, A. *Org. Biomol. Chem.* **2004**, *2*, 2451–2460. (d) Loncaric, C.; Manabe, K.; Kobayashi, S. *Adv. Synth. Catal.* **2003**, *345*, 475–477. (e) Hermitage, S.; Jay, D. A.; Whiting, A. *Tetrahedron Lett.* **2002**, *43*, 9633–9636. (f) Loh, T.-P.; Koh, K. S.-V.; Sim, K.-Y.; Leong, W.-K. *Tetrahedron Lett.* **1999**, *40*, 8447–8451. (g) Kobayashi, S.; Kusakabe, K.; Komiyama, S.; Ishitani, H. *J. Org. Chem.* **1999**, *64*, 4220–4221.

(11) (a) Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J., III; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67–77. (b) Ferraris, D.; Dudding, T.; Young, B.; Drury, W. J., III; Lectka, T. *J. Org. Chem.* **1999**, *64*, 2168–2169. (c) Ferraris, D.; Young, B.; Dudding, T.; Drury, W. J., III; Lectka, T. *Tetrahedron* **1999**, *55*, 8869–8882. (d) Ferraris, D.; Young, B.; Cox, C.; Drury, W. J., III; Dudding, T.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 6090–6091. (e) Drury, W. J., III; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 11006–11007.

Table 1. Cyclization Product Table

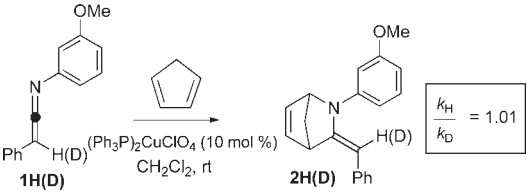
entry[a]	product		yield[b]
1		3a	60
2		3b	65
3		3c	45
4		3d	62
5		3e	63
6		3f	38
7		3g	73

[a] Reaction conditions: PPh_3 (0.1 mmol), $CuClO_4$ (0.05 mmol), 1 mL of CH_2Cl_2, rt, 1 h; then 0 °C, 5 mL of CH_2Cl_2, ketenimine (0.5 mmol), 0.2 mL of cyclopentadiene (3.24 mmol), rt, overnight. [b] All yields are isolated yields.

The ketenimines proved to be fairly unstable and are best prepared immediately before use.[14] Electron withdrawing substituents on the *N*-aromatic ring give products in good yield (entries 2, 5, 6, and 7, Table 1), although when the electron withdrawing character is too potent (i.e., $-NO_2$ groups) the ketenimine becomes quite unstable and condenses with itself. Some electron donating groups can be used with success (entry 3). Interestingly, electron *donating* groups such as 4-methoxy substituents give products in trace amounts regardless of placement on either ring. This result suggests that a "push−pull" mechanism is unlikely. However, placement of one *m*-methyoxy substituent on each ring gave the best yield. It may be the case that increasing the electronegative character of the ketenimine would result in higher yields for cycloaddition products were it not for the basic instability of the ketenimines themselves.

Additionally, if the reaction progresses as envisaged, we should observe a negligible secondary kinetic isotope effect[15] upon cycloaddition of **1D** with enamine formation. In fact, that is exactly what we see when we submit the label isomer **1D** to the reaction and monitor it by ^1H NMR (Scheme 3). Of course, any rate determining pathway involving addition across the C=C bond should exert a normal secondary KIE. A KIE of 1.01 was observed under standard conditions, consistent with a maintenance of hybridization at the vinylic carbon.

Scheme 3. Secondary Isotope Effect Study



In conclusion, we have developed a copper(I) catalyzed Diels−Alder reaction between ketenimines and dienes that proceeds at room temperature. We have observed an enamine intermediate by spectroscopic means that is best explained by a [4 + 2] cycloaddition between the diene and the C=N bond of the ketenimine. Hydrolysis of the enamine upon workup yields products in good yield. Future work will concern an expansion of scope and a detailed mechanistic study.

Acknowledgment. J.E. thanks JHU for a Gary H. Posner Graduate Fellowship.

Supporting Information Available. Experimental procedures, spectroscopic characterization of new compounds, and DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A.; Vreven, T.; Kudin, K. N; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 09*, revision C.B01; Gaussian, Inc.: Wallingford, CT, 2004.

(13) (a) Hratchian, H. P.; Schlegel, H. B. *J. Chem. Theory Comput.* **2005**, *1*, 61–69. (b) Hratchian, H. P.; Schlegel, H. B. In *Theory and Applications of Computational Chemistry: The First 40 Years*; Dykstra, C. E., Frenking, G., Kim, K. S., Scuseria, G., Ed.; Elsevier: Amsterdam, 2005; pp 195–249. (c) Hratchian, H. P.; Schlegel, H. B. *J. Chem. Phys.* **2004**, *120*, 9918–24. (d) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (e) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(14) Ketenimines were prepared by a modified method of McCarthy et al. (ref 6) and used immediately after preparation and titration by ^1H NMR. McCarthy describes the instability of ketenimines, especially the inability to purify diaryl ketenimines by distillation. See Supporting Information for details.

(15) (a) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books; Sausalito, CA, 2006. (b) Giagou, T.; Meyer, M. P. *Chem.—Eur. J.* **2010**, *16*, 10616–10628.

The authors declare no competing financial interest.