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N-Heterocyclic Carbene-Catalyzed Reaction of Chalcones and Enals via Homoenolate: an Efficient Synthesis of 1,3,4-Trisubstituted Cyclopentenes

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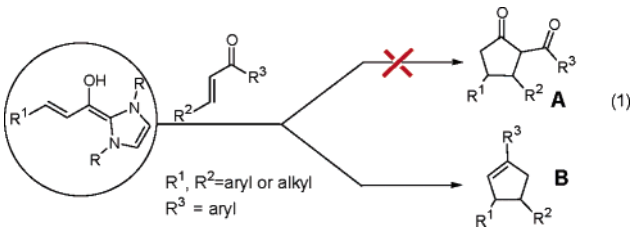
The concept of homoenolate anions was introduced by Nickon and Lambert[1] in their seminal paper in 1962. Their application in organic synthesis during the last four decades, however, was limited, presumably due to the difficulty in generating homoenolates directly. Helquist et al. were the first to circumvent this problem by using β-propionaldehyde anion equivalent as a homoenolate equivalent.[2] Subsequent efforts to generate homoenolate equivalents[3] include the use of β-propionate anion equivalent,[4] cyclopropanone silyl hemiketal,[5] and α-heteroatom-substituted allyl anion by a number of investigators.[3,6] The elegant work on the generation and synthetic uses of chiral homoenolate equivalents, such as 1-hetero-substituted 2-alkenyl-metal derivatives for stereocontrolled homoaldol reactions by Hoppe et al.[7] and Beak and Whisler[8] is especially noteworthy in this context. Very recently, a conceptually new approach to the generation of homoenolate[9] was introduced independently by Bode et al.[9a] and Glorius and Burstein.[9b] This work involves the nucleophilic heterocyclic carbene (NHC)-catalyzed[10−12] annulation of enals with aldehydes, leading to the efficient synthesis of γ-butyrolactones; imines afford the corresponding γ-lactams.[9d] In the course of our work on the reactions of NHCs,[13] we have found that 1,2-diones undergo efficient annulation with enals to afford spiro γ-butyrolactones.[14] Subsequently, we were intrigued by the possibility that the homoenolate annulation, if successful with an activated carbon−carbon double bond such as that of a chalcone, would constitute a cyclopentanone synthesis (eq 1). The results of our work serendipitously leading to a very efficient synthesis of 3,4-*trans*-disubstituted-1-aryl cyclopentenes[15] instead of the expected cyclopentanones are presented in this communication.



(1)

In the first instance, the reaction of 4-methoxy cinnamaldehyde **1** with chalcone **2** in the presence of catalytic amount of 1,3-dimesityl imidazol-2-ylidene (IMes) **3** formed in situ by the deprotonation of IMes chloride (6 mol %) using DBU (12 mol %) afforded a product in 90% yield, and this was characterized as the 1,3,4-trisubstituted cyclopentene **4a** (Scheme 1).

The structure of the product was established by spectroscopic analysis, and final confirmation of the structure and stereochemistry of the compound **4a** was obtained from single-crystal X-ray determination. It is noteworthy that only one diastereomer was formed in this reaction.

Scheme 1. Reaction of 4-Methoxycinnamaldehyde with Chalcone

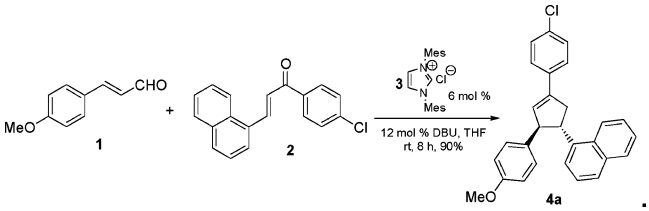
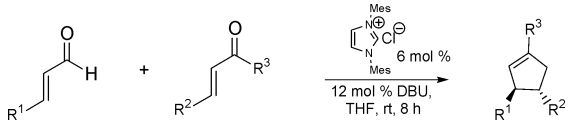


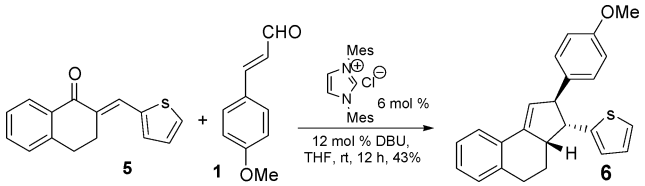
Table 1. Scope of NHC-Catalyzed Cyclopentannulation



entry	R^1	R^2	R^3	product	yield (%)
1	2-MP[b]	2-thienyl	4-chlorophenyl	**4b**	88
2	phenyl	1-naphthyl	4-chlorophenyl	**4c**	76
3	4-MP[b]	2-thienyl	4-methylphenyl	**4d**	85
4	4-MP[b]	4-cyanophenyl	4-chlorophenyl	**4e**	76
5	4-MP[b]	phenyl	phenyl	**4f**	88
6	phenyl	phenyl	phenyl	**4g**	78
7	4-MP[b]	4-fluorophenyl	4-chlorophenyl	**4h**	78
8	4-MP[b]	4-chlorophenyl	4-chlorophenyl	**4i**	76
9	4-MP[b]	2-thienyl	phenyl	**4j**	86
10	4-MP[b]	2-furyl	4-chlorophenyl	**4k**	70
11	4-MP[b]	methyl	4-chlorophenyl	**4l**	55
12	methyl	2-thienyl	4-chlorophenyl	**4m**	73

[a] Isolated yield. [b] MP = methoxy phenyl.

Scheme 2. Reaction of 4-Methoxycinnamaldehyde with Thienylidene Tetralone



The generality of this promising cyclopentannulation was investigated using a number of chalcones and a variety of enals; the results are summarized in Table 1.

Interestingly, the reaction is not limited to β-(hetero)aryl-substituted enones; it occurs efficiently with β-alkyl-substituted enones also (entry 11). Even more interesting is the reaction involving thienylidene tetralone **5** and 4-methoxycinnamaldehyde, leading to tricyclic cyclopentene **6** in moderate yield (Scheme 2). Relative stereochemistry of the product was obtained by ^{1}H NOE difference spectroscopic studies.[16]

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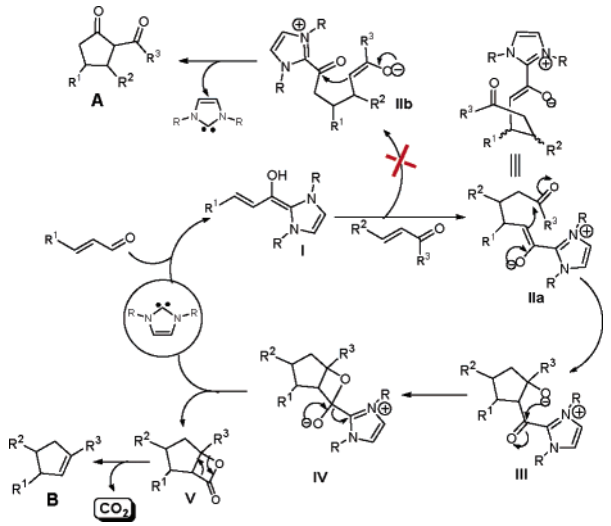
Scheme 3. Postulated Catalytic Cycle Involving NHC



A mechanistic rationale for the reaction may be advanced along the following lines. As might be expected, the homoenolate **I** formed by the reaction of IMes with enal undergoes conjugate addition[17] to the chalcone, followed by proton transfer to generate the enolate **IIa**, which participates in intramolecular aldol reaction to deliver the cyclopentane carbinolate **III**. The latter undergoes beta-lactonization to eject IMes, allowing the catalytic cycle to continue. The β-lactone **V** thus formed is unstable and it undergoes a retro [2+2] process to yield the cyclopentene **B**, with the loss of carbon dioxide (Scheme 3). It is important to mention that aldol lactonization leading to β-lactones has been described in the literature.[18,19] The intermediacy of the β-lactone postulated here can be demonstrated by FTIR spectroscopy. A thin film of the reaction mixture on a NaCl pellet initially displayed the characteristic absorption of the β-lactone at 1822 cm^{-1}(ν_{max}), then a time-dependent depletion of the peak occurs in 45 min. This can be attributed to the elimination of carbon dioxide from β-lactone.[16] The formation of cyclopentene **B** at the exclusion of the expected 2-acyl cyclopentanone **A** may be rationalized by invoking the higher stability of the enolate **IIa** vis a vis **IIb** due to coulombic as well as inductive stabilization offered by the azolium moiety. Thus, the alternate aldol, involving **IIb** leading to cyclopentanone, is not favored.

Although bicyclic β-lactones are known to be unstable,[19a,20] the exceptional instability displayed by the present compounds may be attributed to the bulky substituents, which hamper the disposition of the five-membered ring in the thermodynamically favorable folded envelope conformation. In addition, carbon dioxide elimination will install the styrenic double bond inside the cyclopentane ring, thus rendering it relatively planar. The trans disposition of R^1 and R^2 is not surprising; it is predicated by the transition state for the reaction of the homoenol with the chalcone, reminiscent of the Michael addition of enol/enolate to α,β-unsaturated carbonyl compounds.

In conclusion, we have uncovered a hitherto unknown NHC-catalyzed homoenolate reaction with chalcones, leading to the efficient formation of 1,3,4-trisubstituted cyclopentenes. The simple and mild reaction conditions and the high yields of products are likely to make the reaction attractive for its application in the synthesis of a variety of natural and unnatural cyclopentene derivatives. Further work to define the scope of the reaction and to gain insight into the mechanistic details will be undertaken.

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Supporting Information Available: General experimental procedure, spectroscopic characterization of all new compounds, and single-crystal X-ray data of compound **4a**. This material is available free of charge via the Internet at http://www.pubs.acs.org.

References

(1) Nickon, A.; Lambert, J. L. *J. Am. Chem. Soc.* **1962**, *84*, 4604.
(2) Bal, A. S.; Marfat, A.; Helquist, P. *J. Org. Chem.* **1982**, *47*, 5045.
(3) For reviews on homoenolate anion and their equivalents, see: (a) Lee, V. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 4, p 117 and references therein. (b) Werstiuk, N. H. *Tetrahedron* **1983**, *39*, 205.
(4) Lombaert, S. D.; Lesur, B.; Ghosez, L. *Tetrahedron Lett.* **1982**, *23*, 4251.
(5) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056.
(6) Selected references: (a) Binns, M. R.; Haynes, R. K. *J. Org. Chem.* **1981**, *46*, 3790. (b) Hirama, M. *Tetrahedron Lett.* **1981**, *22*, 1905. (c) Krams, G. A.; Fraizier, K. *Synth. Commun.* **1978**, *8*, 483. (d) Sanchez, I. H.; Aguilar, A. M. *Synthesis* **1981**, 55. (e) Haynes, R. K.; Katsifis, A. G.; Vonwiller, S. C.; Hambley, T. W. *J. Am. Chem. Soc.* **1988**, *110*, 5423. (f) Hua, D. H.; Venkataraman, S.; Ostrander, R. A.; Gurudas, S. Z.; McCann, P. J.; Coulter, M. J.; Xu, M. R. *J. Org. Chem.* **1988**, *53*, 507 and references therein. (g) Ahlbrecht, H.; Dietz, M.; Weber, L. *Synthesis* **1987**, 251.
(7) Özlügedik, M.; Kristensen, J.; Wibbeling, B.; Fröhlich, R.; Hoppe, D. *Eur. J. Org. Chem.* **2002**, 414. For recent examples, see: (a) Seppi, M.; Kalkofen, R.; Reupohl, J.; Fröhlich, R.; Hoppe, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 1423. (b) Reuber, J.; Fröhlich, R.; Hoppe, D. *Org. Lett.* **2004**, *6*, 783.
(8) Whisler, M. C.; Beak, P. *J. Org. Chem.* **2003**, *68*, 1207.
(9) (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370. (b) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205. (c) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905. (d) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131. (e) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506.
(10) For the origin of NHC chemistry and its catalytic reactivity, see: Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719. For the isolation of stable NHCs, see: (a) Arduengo, A. J., III; Harlow, R. L.; Kline, M. K. *J. Am. Chem. Soc.* **1991**, *113*, 361. (b) Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J.-P.; Ebel, K.; Brode, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1021.
(11) For reviews, see: (a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534. (b) Nair, V.; Bindu, S.; Sreekumar, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 5130.
(12) (a) Singh, R.; Kissling, R. M.; Letellier, M.-A.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 209. (b) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298. (c) Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743. (d) Reynolds, N. T.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 16406. (e) Christmann, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2632.
(13) (a) Nair, V.; Sreekumar, V.; Bindu, S.; Suresh, E. *Org. Lett.* **2005**, *7*, 2297. (b) Nair, V.; Bindu, S.; Sreekumar, V.; Rath, N. P. *Org. Lett.* **2003**, *5*, 665.
(14) Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett.* **2006**, *8*, 507.
(15) (a) Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906. (b) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (c) Lu, X.; Lu, Z.; Zhang, X. *Tetrahedron* **2006**, *62*, 457. (d) Wison, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1426.
(16) See Supporting Information for details.
(17) (a) Crimmins, M. T.; Nantermet, P. G. *J. Org. Chem.* **1990**, *55*, 4235. (b) Crimmins, M. T.; Nantermet, P. G.; Trotter, B. W.; Vallin, I. M.; Watson, P. S.; McKerlie, L. A.; Reinhold, T. L.; Cheung, A. W.-H.; Stetson, K. A.; Dedopoulou, D.; Gray, J. L. *J. Org. Chem.* **1993**, *58*, 1038.
(18) (a) Wynberg, H.; Staring, E. G. *J. Am. Chem. Soc.* **1982**, *104*, 166. (b) Wynberg, H.; Staring, E. G. *J. Org. Chem.* **1985**, *50*, 1977.
(19) (a) Cortez, G. S.; Tennyson, R. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123*, 7945. (b) Yokota, Y.; Cortez, G. S.; Romo, D. *Tetrahedron* **2002**, *58*, 7075. (c) Oh, S. H.; Cortez, G. S.; Romo, D. *J. Org. Chem.* **2005**, *70*, 2835.
(20) Goldschmidt, Z.; Antebi, S. *Tetrahedron Lett.* **1978**, *19*, 1225.

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