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Novel Nucleophilic Heterocyclic Carbene Mediated Stereoselective Conjugate Addition of Enals to Nitrostyrenes via Homoenolate§

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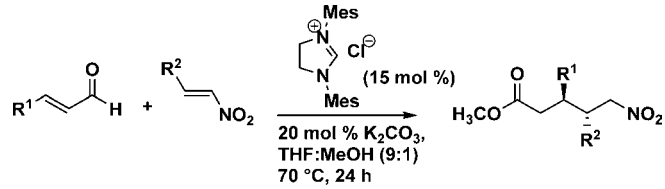
ABSTRACT



A stereoselective Michael addition of homoenolate, generated from enals by nucleophilic heterocyclic carbene (NHC) catalysis, to *β*-nitrostyrenes is reported for the first time. The products of this reaction obtained in good yields are of potential value in the synthesis of a variety of acyclic and heterocyclic compounds.

The advent of homoenolate[1] as a reactive intermediate and its recognition as a three-carbon synthon with potential application in organic synthesis[2] attracted the attention of a number of research groups during the last three decades. Early work in this area, however, relied exclusively on homoenolate equivalents[3] since no direct route was available for the generation of this species. The homoenolate equivalents that have been used with varying degrees of success include cyclopropanone acetals,[4] Grignard reagents derived from *β*-bromoacetals,[5] and the versatile metallo-allyl carbamates.[6] A radically different approach to the generation of homoenolate which utilizes the reactivity inversion (umpolung) of enals akin to the formation of enaminal (Breslow intermediate[7]) from aldehydes and nucleophilic heterocyclic carbene[8] (NHC) was introduced by Bode[9] and Glorius,[10] independently, in 2004. Since then, this protocol has found general acceptance, and a number of novel

§ Dedicated with best wishes to Professor Gilbert Stork.

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(1) Nickon, A.; Lambert, J. L. *J. Am. Chem. Soc.* **1962**, *84*, 4604.

(2) For a recent review of homoenolate in organic syntheis, see: Nair, V.; Vellalth, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691.

(3) For a review of homoenolate equivalents, see: Kuwajima, I.; Nakamura, E. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991.

(4) (a) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 7360. (b) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056. (c) Nakamura, E.; Kuwajima, I. *Org. Synth.* **1988**, *66*, 43.

(5) Bal, A. S.; Marfat, A.; Helquist, P. *J. Org. Chem.* **1982**, *47*, 5045.

(6) (a) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932. (b) Zschage, S.; Hoppe, D. *Tetrahedron* **1992**, *48*, 5657. (c) Hoppe, D. *Synthesis* **2009**, 43.

(7) (a) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719. (b) Zhao, H.; Foss, F. W., Jr.; Breslow, R. *J. Am. Chem. Soc.* **2008**, *130*, 12590.

(8) For recent reviews of NHC chemistry see: (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (b) Marion, N.; Diez-Gonzalez, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988. (c) Nair, V.; Bindu, S.; Sreekumar, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 5130. (d) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506.

(9) (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370.

(10) (a) Burstein, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 6205. (b) Burstein, C.; Tschan, S.; Xie, X. L.; Glorius, F. *Synthesis* **2006**, 2418.

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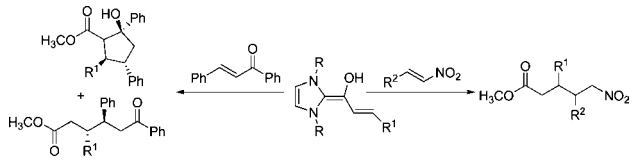
reactions leading to the synthesis of γ-lactones,[8,9] γ-spirolactones,[11] lactams,[12] cyclopentenes,[13,14] cyclopentanones,[15] and related products have been described in the recent literature.

In the context of our recent observation of the formation of cyclopentanes and related organic compounds in the reaction of homoenolates with chalcones in methanol,[16,17] it was of interest to investigate the prospect of homoenolate addition to nitroalkenes. Evidently, the latter are unique Michael acceptors endowed with the most powerful electron-withdrawing group (EWG), which is amenable to a variety of synthetic transformations.[18,19] A successful Michael addition[20,21] of homoenolate to β-nitroalkene as envisioned above would provide access to potentially useful functionalized five-carbon synthons (Scheme 1). It is noteworthy that

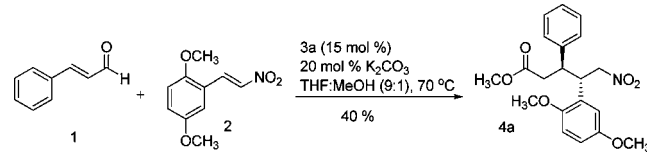
Scheme 1. Background and Concept



such a reaction would constitute the first example of Michael reaction of homoenolate with nitroalkene.[22]

Against the above backdrop, in a pilot experiment, cinnamaldehyde and 2,5-dimethoxy-β-nitrostyrene were exposed to imidazolin-2-ylidene, generated from catalytic amount of imidazolium chloride **3a**, by potassium carbonate in THF−methanol. The reaction mixture was processed after 24 h, and the crude product on purification by chromatography afforded a crystalline solid **4a** as the major product (Scheme 2). The structure of the latter was assigned on the

Scheme 2



basis of spectroscopic data. Conclusive evidence for the structure and stereochemistry of **4a** was obtained from single-crystal X-ray analysis (Figure 1).

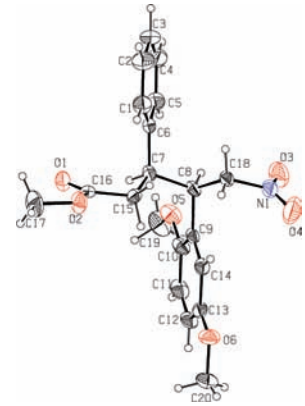


Figure 1. ORTEP diagram of **4a**.

In view of the success of the reaction, it was obligatory to assess the usefulness of other commonly available NHC catalysts in this reaction. A number of experiments were conducted, and the results are summarized in Table 1. Among the four catalysts investigated, imidazolinium catalyst **3b**[23] gave the best results. The benzimidazolium catalyst **3c** gave

(11) (a) Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett.* **2006**, *8*, 507. (b) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E.; Viji, S. *Synthesis* **2007**, 3195.

(12) (a) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131. (b) He, M.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 418.

(13) (a) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736.

(14) For related work by other groups see: (a) Chiang, P. C.; Kaeobamrung, J.; Bode, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 3520. (b) Wadamoto, M.; Philips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 10098.

(15) (a) Nair, V.; Babu, B. P.; Vellalath, S.; Suresh, E. *Chem. Commun.* **2008**, 747.

(16) Nair, V.; Babu, B. P.; Vellalath, S.; Varghese, V.; Raveendran, A. E.; Suresh, E. *Org. Lett.* **2009**, *11*, 2507.

(17) For earlier work on homoenolates in protic solvents, see: (a) Chan, A.; Schiedt, K. A. *Org. Lett.* **2005**, *7*, 905. (b) Maki, B. E.; Chan, A.; Schiedt, K. A. *Synthesis* **2008**, 1306. (c) Sohn, S. S.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3873.

(18) (a) Czekelius, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 612. (b) Calderari, G.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1592. (c) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001. For reviews, see: (d) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933.

(19) (a) Nef, J. U. *Justus Liebigs Ann. Chem.* **1894**, *280*, 263. (b) Pinnick, H. W. *Org. React.* **1990**, *38*, 655. (c) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989. (d) Beck, A. K.; Seebach, D. *Chem. Ber.* **1991**, *124*, 2897. (e) Maeri, R. E.; Heinzer, J.; Seebach, D. *Liebigs Ann.* **1995**, 1193. (f) Poupart, M. A.; Fazal, G.; Goulet, S.; Mar, L. T. *J. Org. Chem.* **1999**, *64*, 1356. (g) Barrett, A. G. M.; Spilling, C. D. *Tetrahedron Lett.* **1988**, *29*, 5733. (h) H. Loyd, D.; Nichols, D. E. *J. Org. Chem.* **1986**, *51*, 4294.

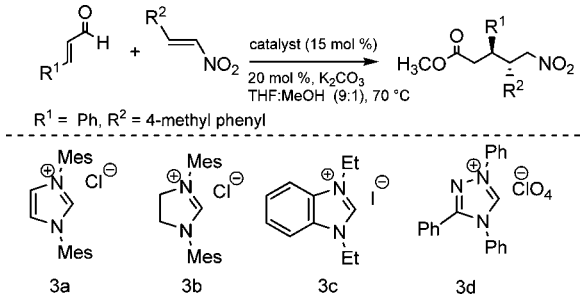
(20) For reference to Michael addition of a varity of nucleophiles to nitroalkenes, see: (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergmon press: New York, 1992. (b) Enders, D.; Forster, D.; Raabe, G.; Bats, J. W. *J. Org. Chem.* **2008**, *73*, 9641. (c) Johnson, T. A.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 1004. (d) Alza, E.; Cambeiro, X. C.; Jimeno, C.; Pericas, M. A. *Org. Lett.* **2007**, *9*, 3717. (e) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (f) Rimkus, A.; Sewald, N. *Org. Lett.* **2002**, *4*, 3289. (g) Hong, B. C.; Nimje, R. Y.; Wu, M. F.; Sadani, A. A. *Eur. J. Org. Chem.* **2008**, 1449.

(21) For asymmetric Michael addition to nitroalkenes, see:(a) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, *12*, 1877. (b) Gracia, P. G.; Ladepeche, A.; Halder, R.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 4719. (c) Hayashi, Y.; Itoh, T.; Ohkubo, M.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4722. (d) Trost, B. M.; Hitce, J. *J. Am. Chem. Soc.* **2009**, *131*, 4572.

(22) (a) While this manuscript was in preparation. a report on the asymmetric Stetter reaction of aldehydes to β-nitrostyrene was published: DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 10872. For earlier work on the asymmetric Michael addition of acyl anion equivalent to nitroalkene, see: (b) Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4932.

(23) As far as we know, **3b** has not been used as a catalyst in homoenolate reaction previously.

Table 1. Catalyst Screening



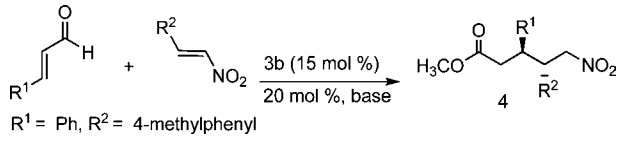
entry	catalyst	condition	yield (%)[a]
1	**3a**	THF:MeOH (9:1), 70 °C, 24 h	56
2	**3b**	THF:MeOH (9:1), 70 °C, 24 h	70
3	**3c**	THF:MeOH (9:1), 70 °C, 24 h	20
4	**3d**	THF:MeOH (9:1), 70 °C, 36 h	–

[a] Overall yield.

low yield of the product, while the triazolium catalyst, **3d**, was completely ineffective. Although it is not possible to rationalize the superior perfomance of **3b** vis a vis other catalysts, it is notworthy that **3b** is the most nucleophilic one in this group.

With a view to optimize the yield of the product, we studied the influence of different bases in generating the NHC catalyst, and the results are shown in Table 2. Interestingly,

Table 2. Optimization



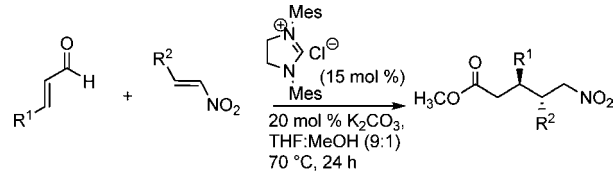
entry	base	condition	yield[a] %
1	DBU	THF:MeOH (9:1), 70 °C, 24 h	–
2	K_2CO_3	THF:MeOH (9:1), 70 °C, 24 h	70
3	$CsCO_3$	THF:MeOH (9:1), 70 °C, 24 h	34
4	Na_2CO_3	THF:MeOH (9:1), 70 °C, 24 h	37
5	$BaCO_3$	THF:MeOH (9:1), 70 °C, 24 h	–
6	Li_2CO_3	THF:MeOH (9:1), 70 °C, 24 h	–
7	K_2CO_3	THF:MeOH (7:2), 70 °C, 24 h	56
8	K_2CO_3	THF:MeOH (1:1), 70 °C, 24 h	34
9	K_2CO_3	THF:MeOH (1:1), rt, Ar, 24 h	–
10	K_2CO_3	THF, 70 °C, 24 h	–
11	K_2CO_3	MeOH, 70 °C, 24 h	–
12	K_2CO_3	Toluene:MeOH (7:2), 70 °C, 24 h	15

[a] Overall yield.

the best results were obtained with potassium carbonate in THF/MeOH (9:1).

After having reasonably established the optimum parameters, the reaction was extended to a number of nitroalkenes, and the results are summarized in Table 3. In our studies,

Table 3. Scope of the Reaction[a]



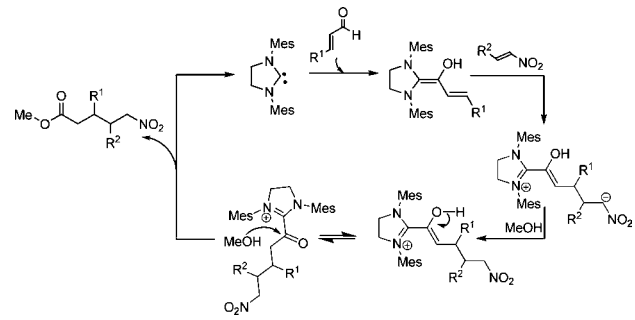
entry	R^1	R^2	products	yield % (dr)
1	phenyl	2,5-dimethoxyphenyl	**4a**	50 (5:1)
2	phenyl	2-furyl	**4b**	70 (15:1)
3	phenyl	4-methylphenyl	**4c**	70 (10:1)
4	phenyl	2-thienyl	**4d**	63 (10:1)
5	phenyl	4-methoxy phenyl	**4e**	63 (10:1)
6	phenyl	4-fluorophenyl	**4f**	63 (5:1)
7	4-methoxy phenyl	phenyl	**4g**	61 (10:1)
8	phenyl	1-naphthyl	**4h**	60 (3:1)
9	2-methoxy phenyl	4-methylphenyl	**4i**	57 (6:1)
10	4-methoxy phenyl	4-methylphenyl	**4j**	53 (10:1)
11	4-methoxy phenyl	1-naphthyl	**4k**	47 (5:1)
12	phenyl	4-chlorophenyl	**4l**	40 (3:1)

[a] dr is determined by ^{1}H NMR analysis.

useful yields of products were obtained only with aryl-substituted enals and β-nitrostyrenes.

Mechanistically the reaction may be viewed as involving the initial formation of homoenolate by the reaction of NHC with the enal followed by its Michael addition to β-nitrostyrene, and the stereoselectivity observed in the product formation may be attributed to the trans selective Michael addition (Scheme 3).

Scheme 3. Mechanistic Postulate for the Formation of **4**



In conclusion, the first report on the efficient, NHC-catalyzed, stereoselective Michael addition of enals to

(24) (a) Mohaboobi, S.; Eibler, E.; Koller, M.; Sunilkumar, K C.; Popp, A. *J. Org. Chem.* **1999**, *64*, 4697. (b) Pei, Z.; Li, X.; von Geldern, T. W.; Longenecker, K.; Pireh, D.; Stewart, K. D.; Backes, B. J.; Lai, C.; Lubben, T. H.; Ballaron, S. J.; A. Beno, D. W.; Kempf-Grote, A. J.; Sham, H. L.; Trevillyan, J. M. *J. Med. Chem.* **2007**, *50*, 1983.

β-nitrostyrenes via the intermediary homoenolate is presented in this communication. It is reasonable to assume that since the products are doubly functionalized five carbon synthons this reaction will find application in organic synthesis, especially in the synthesis of biologically active pyrrolidinone and piperidone derivatives.[24]

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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