Synthetic Communications[®], 37: 2337–2343, 2007 Copyright © Taylor & Francis Group, LLC ISSN 0039-7911 print/1532-2432 online DOI: 10.1080/00397910701410814



MgBr₂-Mediated Ionic Diels–Alder Reaction of Acetals of α , β -Unsaturated Aldehydes and Ketones with 1,3-Dienes

Subhash P. Chavan, Krishna S. Ethiraj, and Shubhada W. Dantale Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune, India

Abstract: A facile, mild, and efficient methodology for the ionic Diels–Alder reaction of acetals of α , β -unsaturated ketones and aldehydes as dienophiles with various 1,3-dienes employing MgBr₂ as the Lewis acid catalyst to furnish corresponding Diels–Alder adducts at ambient temperature is described.

Keywords: acetals, catalysts, Diels-Alder reactions, dienes

The Diels–Alder reaction is one of the most efficient and widely utilized reactions for the stereoselective construction of six-membered rings. Often the Diels–Alder reactions employ harsh conditions, thereby leading to polymerization of dienes and dienophiles. A variety of modified methods have been proposed in the Diels–Alder cycloadditions to overcome problems such as polymerization and isomerization encountered in the thermal reactions. Lewis acids,^[1] certain lanthanide complexes,^[2] and high-pressure techniques^[3] have been utilized to avoid polymerization and isomerization.

Highly reactive dienophiles such as acrolein and methyl vinyl ketone often undergo polymerization even at low temperature. However, they are stable

Received in the USA December 4, 2006

Address correspondence to Subhash P. Chavan, Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune 411 008, India. E-mail: sp. chavan@ncl.res.in

when stored as corresponding acetals. Normally α,β -unsaturated acetals require high temperatures for cycloaddition reactions. However, in the presence of a suitable reagent, they can be made to undergo facile cycloaddition via the intermediacy of allyl cations,^[4] which serve as strong dienophiles.

Ionic Diels–Alder reactions of acetals of α,β -enones and α,β -enals with various 1,3-dienes has been reported, employing triflic acid dissolved in 1,1,2-trichloro-1.2,2-trifluoro ethane,^[4] electrogenetrated acid,^[5] TiCl₄ with Ti(Oi-Pr)₄,^[6] and LiClO₄ with 1 mol% camphor sulphonic acid.^[7] In addition, reactions of triethylorthopropiolate^[8] or triethyl orthoacrylate^[9] to 1,3-dienes using trimethylsilyl triflate to furnish the corresponding cycloadducts are also well documented. Cycloaddition of 1-vinyl-4-methyl-2,6,7-trioxabicy-clo[2.2.2]octane to 1,3-dienes has been carried out using BF₃(OEt)₂.^[10] Lewis acids such as TiCl₄, Me₃SiOTf, BF₃(OEt)₂. SnCl₄, and GaCl₃ have also been employed for the generation of highly reactive cationic dienophiles from 2,2-dimethoxyethyl acrylates for ionic Diel–Alder reaction with various 1,3-dienes.^[11-15] Recently Nafion-H^[16a] and InCl₃^[16b] have been shown to be excellent catalysts in ionic Diels–Alder reactions. Most of these methods employ expensive reagents and require the reactions to be performed at low temperatures.

We have recently demonstrated that FeCl₃^[17a] and I₂^[17b] act as efficient catalysts in effecting ionic Diels–Alder reactions. Our search for milder and efficient reagents led us to explore the utility of MgBr₂ as the Lewis acid in effecting ionic Diels–Alder reaction. This communication describes a facile Diels–Alder reaction of various 1,3-dienes with acetals of α , β -unsaturated ketones and aldehydes using MgBr₂ as an efficient catalyst in good yields.

The oxophilic propensity of MgBr₂ is well documented.^[18,19] It was decided to exploit this propensity of MgBr₂ in complexing with the oxygen of the acetal, thereby transiently generating the allyl cation, which would undergo a Diels–Alder reaction. Initial experiments were carried out with cyclopentadiene and acrolein acetal **1**. Thus, cyclopentadiene was subjected to the Diels–Alder reaction with acrolein acetal with MgBr₂ as the Lewis acid.

After a few trials varying the amount of catalyst, solvent, and temperature, it was concluded that the best results were obtained when the reaction was performed with 0.5 eq. of MgBr₂ and dichloromethane as the solvent.

Accordingly, freshly prepared MgBr₂ (from dibromoethane and Mg) treated with a mixture of cyclopentadiene **5** and acrolein acetal **1** was allowed to stir at room temperature in dichloromethane as the solvent and, after usual workup, furnished the cycloadduct **6** in 80% yield as a mixture of stereoisomers (*endo:exo* = 6:1).

Having successfully demonstrated the utility of $MgBr_2$ as an efficient Lewis acid in effecting ionic Diels–Alder reaction, attention was focused on establishing the generality of this reaction. Accordingly, cyclic and acyclic dienes were subjected to the reaction with different dienophiles, and moderate to good yields of the corresponding adducts were obtained. The results of this study are summarized in Table 1.

2338

Entry	Diene	Dienophile	Product	Time (h)	Yield (%)
1	5		6 × 0 0	4	80 (6:1)
2	7		8,00	4	65 ^a
3	9			12	38 ^{b,c}
4	5		11 ² 7 0	8	50 (3.8:1)
5	5		12 200	8	68 (3.3:1)
6	7		13	2	72 ^a
7	9	↓ ↓ ₃		12	61 ^{<i>b</i>,<i>c</i>}

Table 1. Cycloaddition reactions of dienes and dienophiles using MgBr₂ as catalyst

(continued)

Entry	Diene	Dienophile	Product	Time (h)	Yield (%)
8	5	OEt OEt 4	15 / OEt Eto	8	66

Table 1. Continued

Note. Reaction was carried out with 0.5 eq of $MgBr_2$ in dichloromethane at room temperature.

^{*a*}Single isomer.

^b10 eq. of the diene were used.

 $^{\mathrm{c}}\text{Reaction}$ mixture was initially maintained at 0°C, then allowed to attain room temperature.

From the table, it is clear that cyclic dienes participate well as compared to the acyclic dienes. This may be ascribed to the greater reactivity of the cyclic dienes than the reactivity of the acyclic one. Variously substituted α,β -unsaturated acetals (1-4) were also subjected to ionic Diels-Alder reactions. They were shown to participate well in the ionic Diels-Alder reaction. An interesting point worthy of note is the exclusive formation of the *endo* isomer when the reaction was performed with cyclohexadiene and acetals 1 and 3. The acyclic diene isoprene (9) furnished only one regioisomer when subjected to the treatment with acetals 1 and 3 (Table 1, entries 3 and 7). It is interesting to note that the acyclic acetal 4 gives less yield of the cyclo-adduct than cyclic acetal 1 (Table 1, entries 1 and 8). This may be ascribed to the removal of ethanol from the ionic intermediate, thereby resulting in low efficiency of recombination and hence lower yield.

In conclusion, we have demonstrated $MgBr_2$ as a convenient, simple, and efficient reagent to achieve high levels of stereoselective and regioselective ionic Diel-Alder reactions at ambient temperature. Currently, we are exploring the use of other homogeneous and heterogeneous materials to effect such transformation under mild conditions.

EXPERIMENTAL

1. General Procedure for Ionic Diels-Alder Reaction

To the freshly prepared MgBr₂ (0.5 eq.) in 10 ml of dry CH_2Cl_2 under a nitrogen atmosphere, first 2 eq./10 eq. of 1,3-diene was added, followed by 1 eq. of dienophile (unsaturated acetal) in 1 ml of dry CH_2Cl_2 . (In the case of isoprene, temperature was lowered to 0°C). The reaction mixture was

MgBr₂-Mediated Ionic Diels-Alder Reaction

stirred at room temperature and monitored by thin-layer chromatagraphy (TLC). After the completion of reaction, it was quenched with 15 ml of water and stirred until it became clear. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 ml). The organic layer was dried with anhydrous Na_2SO_4 , and concentration under reduced pressure furnished a viscous residue. Column purification of the residue on SiO_2 /neutral alumina furnished the Diels–Alder adduct as a viscous oil in good yields.

2. Typical Procedure for the Preparation of 8

MgBr₂ was prepared from 30 mg of magnesium turnings (1.25 mmol) and 0.47 g (2.5 mmol) of 1,2-dibromoethane. To the freshly prepared MgBr₂ (1.25 mmol) in 10 ml of dry CH₂Cl₂, 0.40 g (5 mmol) of 1,3-cyclohexadiene **7** was added, followed by 0.25 g (2.5 mmol) of 2-vinyl-1,3-dioxalane **1**. The reaction was stirred at room temperture for 4 h and monitored by thin-layer chromatography (TLC). After completion of the reaction and usual workup, followed by purification by column chromatography (SiO₂) using 2% ethyl acetate-pet. Ether as eluent, the reaction furnished 0.29 g of *endo*-2(bicy-clo[2.2.2]oct-5-en-2-yl) dioxolane **8** as a viscous oil in 65% yield.

IR (neat) cm⁻¹: 3075, 1975, 1330, 1120, 975, 840. ¹H NMR (200 MHz): 1.15–1.4 (m, 2H), 1.40–1.85 (m, 4H), 1.85–1.95 (m, 1H), 2.55 (br s, 1H), 2.70 (br d, 1H), 3.75–4.05 (m, 4H), 4.35 (d, 1H, J = 10.8 Hz), 6.20 (dd, 1H, J = 5.4), 6.40 (dd, 1H, J = 5.4). Mass (m/e): 180, 151, 137, 99, 79, 77, 73, 65, 55. All compounds were characterized by ¹H NMR, ¹³C NMR, and mass spectral analyses.

ACKNOWLEDGMENTS

Presented in part at the National Symposium in Chemistry, January 27-30, 1999, Indian Institute of Science (IISc). Banglore, India. One of us (K. S. Ethiraj) thanks Council of Scientific and Industrial Research (CSIR), New Delhi (India), for the award of a fellowship. Funding under Young Scientist Award (YSA) scheme from CSIR, India, is gratefully acknowledged. We are thankful to T. Ravindranathan for encouragement.

REFERENCES

 (a) Yates, P.; Eaton, P. Acceleration of the Diels-Alder reaction by aluminum chloride. J. Am. Chem. Soc. 1960, 82, 4436; (b) Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. Chiral (acyloxy)borane (CAB): A powerful and practical catalyst for asymmetric Diels-Alder reactions. J. Org. Chem. 1989, 54, 1481-1483.

S. P. Chavan, K. S. Ethiraj, and S. W. Dantale

- (a) Bednarski, M.; Danishefsky, S. On the interactivity of chiral auxiliaries with chiral catalysts in the hetero Diels–Alder reaction: A new route to L-glycolipids. *J. Am. Chem. Soc.* **1983**, *105*, 6968; (b) Danishefsky, S.; Bednarski, M. Catalysis of homo Diels–Alder reactions by Yb(fod)₃. *Tetrahedron Lett.* **1985**, *26*, 2507–2508.
- (a) Dauben, W. G.; Krabbenhoft, H. O. Organic reactions at high pressure: Cycloadditions with enol and dienol derivatives. J. Org. Chem. 1977, 42, 282;
 (b) Matsumoto, K.; Sera, A. Organic synthesis under high pressure II. Synthesis 1985, 999;
 (c) Uyehara, T.; Yamamoto, Y. J. Synth. Org. Chem. Jpn. 1989, 47, 321 and references cited therein.
- Gassman, P. G.; Singleton, D. A.; Wilwerding, J. J.; Chavan, S. P. Acrolein acetals as allyl cation precursors in the ionic Diels–Alder reaction. *J. Am. Chem. Soc.* 1987, 109, 2182.
- 5. Inokuchi, T.; Tanigawa, S.-I.; Toru, S. An endo-selective ionic Diels-Alder reaction of α,β -enone and α,β -enal acetals catalyzed by electrogenerated acid. *J. Org. Chem.* **1990**, *55*, 3958.
- Sammakia, T.; Berliner, M. A. Asymmetric Diels–Alder reactions with α,β-unsaturated acetals. J. Org. Chem. 1994, 59, 6890.
- Grieco, P. A.; Collins, J. L.; Handy, S. T. Acid catalysed ionic Diels–Alder in concentated solutions of lithium perchlorate in diethyl ether. *Synlett* 1995, 1155.
- 8. Gassman, P. G.; Chavan, S. P.; Fertel, L. B. The $2\pi + 2\pi$ cycloaddition of an allyl cation to (1Z,3E)-cycloalkadienes: Evidence for a stepwise process in the ionic Diels-Alder reaction. *Tetrahedron Lett.* **1990**, *31*, 6489.
- Gassman, P. G.; Chavan, S. P. Ethynyl ortho esters as precursors of propargyl cations: The low-temperature, ionic Diels-Alder addition of ethyl propiolate to 1,3-dienes via ethynyl ortho esters. *Tetrahedron Lett.* **1988**, *29*, 3407.
- Gassman, P. G.; Chavan, S. P. The low-temperature, ionic Diels–Alder addition of vinyl ortho esters to 1,3-dienes. J. Org. Chem. 1988, 53, 2392.
- Gassman, P. G.; Chavan, S. P. The ionic Diels-Alder reaction of 1-vinyl-4methyl-2,6,7-trioxabicyclo[2.2.2]octane: Retention of the ortho ester moiety through the use of the trioxabicyclo[2.2.2]octanyl protecting group. J. Chem. Soc., Chem. Commun. 1989, 13, 837.
- Hashimoto, Y.; Nagashima, T.; Kobayashi, K.; Hasegawa, M.; Saigo, K. Mild and efficient Diels–Alder reaction using cationic dienophiles generated *in situ*. *Tetrahedron* **1993**, *49*, 6349.
- 13. Provilhes, A.; Uriarte, E.; Kouklovsky, C.; Langlois, N.; Langlois, Y.; Chiaroni, A.; Richie, C. Chiral α,β -unsaturated oxazolines in the asymmetric Diels–Alder reaction. *Tetrahedron Lett.* **1989**, *30*, 1395.
- Jung, M. E.; Vaccaro, W. D.; Buszek, K. R. Asymmetric Diels–Alder reactions of chiral alkoxy iminium salts. *Tetrahedron Lett.* 1989, 30, 1893.
- Kitagawa, O.; Aoki, K.; Inove, T.; Taguchi, T. Diels–Alder reaction of *N*-allylic enamides and lactam derivatives through iodine mediated activation. *Tetrahedron Lett.* 1995, 36, 593.
- (a) Vankar, P. S.; Reddy, M. V.; Kumareswaran, R.; Pitre, S. V.; Roy, R.; Vankar, Y. D. Studies in Lewis acid and LiClO₄ (or Nafion-H) catalysed ionic Diels-Alder reactions of chiral and achiral olefinic acetals respectively. *Tetrahedron* 1999, *55*, 1099; (b) Reddy, G.; Kumareswaran, R.; Vankar, Y. D. Indium trichloride: A useful catalyst for ionic Diels-Alder reactions. *Tetrahedron Lett.* 2000, *41*, 10333.
- 17. (a) Chavan, S. P.; Sharma, A. K. Use of FeCl₃ and FeCl₃ adsorbed on silica as efficient Lewis acid catalyst in ionic Diels–Alder reactions of α , β -unsaturated acetals. *Synlett* **2001**, *5*, 667–669; (b) Chavan, S. P.; Sharma, P.; Ramakrishna, G.;

2342

MgBr₂-Mediated Ionic Diels-Alder Reaction

Thakkar, M. I₂ as an efficient catalyst in ionic Diels–Alder reactions of α , β -unsaturated acetals. *Tetrahedron Lett.* **2003**, *44* (14), 3001–3003.

- 18. Kim, S.; Park, J. H. Selective removal of tetrahydropyranyl ethers in the presence of tert-butyldimethylsilyl ethers with magnesium bromide in ether. *Tetrahedron Lett.* **1987**, 28, 439.
- Basavaiah, P.; Bhavani, A. K. D.; Pandiyaraju, S.; Sarma, P. K. S. Baylis–Hilman reaction: Magnesium bromide as a stereoselective reagent for the synthesis of [E]-[Z]-allyl bromides. *Synlett* **1995**, *3*, 243.

Copyright of Synthetic Communications is the property of Taylor & Francis Ltd and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.