Available online at www.sciencedirect.com

ScienceDirect

Tetrahedron Letters 48 (2007) 1577–1579

Tetrahedron Letters

Montmorillonite clay-catalyzed hetero-Diels–Alder reaction of 2,3-dimethyl-1,3-butadiene with benzaldehydes

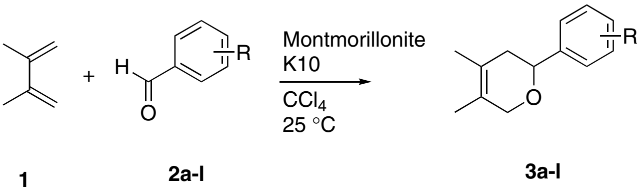
Matthew R. Dintzner,* Andrew J. Little, Massimo Pacilli, Dominic J. Pileggi, Zachary R. Osner and Thomas W. Lyons

Department of Chemistry, DePaul University, 1036 West Belden Ave., Chicago, IL 60614, United States

Received 7 September 2006; revised 18 December 2006; accepted 3 January 2007
Available online 7 January 2007

Abstract—Montmorillonite K10 clay was found to catalyze the hetero-Diels–Alder reaction of 2,3-dimethyl-1,3-butadiene with *o*-anisaldehyde and other benzaldehyde derivatives; a transition state involving chelation of the clay's metal ions with the dienophile's heteroatoms is proposed.

Construction of the dihydropyran ring system via hetero-Diels–Alder reactions that employ aldehydes as dienophiles is well precedented and has been featured in the synthesis of a wide variety of natural products.[1,2] There have been numerous reports on the hetero-Diels–Alder reaction of aldehydes with activated dienes (such as Danishefsky's diene and the like) or with nonactivated simple dienes under forced conditions.[3] The reaction of aldehydes with simple, nonactivated dienes under mild conditions, however, is much less well precedented, and the use of electron-rich benzaldehydes as dienophiles has not been reported.[4] Herein we describe a novel, Montmorillonite clay-catalyzed hetero-Diels–Alder reaction of *o*-anisaldehyde and other benzaldehyde derivatives with 2,3-dimethyl-1,3-butadiene (**1** + **2**→**3**, Scheme 1).



Scheme 1. Montmorillonite clay-catalyzed hetero-Diels–Alder reaction.

A recent work in our laboratories has shown that Montmorillonite clays are effective natural catalysts for the synthesis of heterocyclic compounds like benzopyrans[5] and chromenes[6] under mild conditions. In an effort to further broaden the repertoire of applications of clays as environmentally benign catalysts for organic reactions, we investigated the hetero-Diels–Alder reaction of 2,3-dimethyl-1,3-butadiene (**1**) with benzaldehyde derivatives (**2a**–**l**). Preliminary experiments, which were conducted with benzaldehyde (1.1 mmol) and 2,3-dimethyl-1,3-butadiene (1.0 mmol) in refluxing carbon tetrachloride with Montmorillonite K10 clay (1 equiv by weight), were minimally encouraging. Only about 10% conversion to the desired Diels–Alder adduct was observed, along with unreacted benzaldehyde and dimerized diene. We found that preheating the clay to 110 °C for 1 h prior to conducting the reaction made for a more active Lewis acid catalyst and resulted in an improved conversion of reactants to the desired Diels–Alder adduct, though dimerization was still a competing side reaction. Heating the clay to even higher temperatures (200 °C, 1 h) provided an even more active catalyst, presumably due to the collapse of the clay's interlayer structure as water is extruded, with subsequent decrease in Bronsted acidity and increase in Lewis acidity.[7] We found that this more activated clay promoted much better conversion to the desired product and successfully suppressed dimerization of the diene.

We next surveyed a variety of substituted benzaldehydes to determine the reaction scope (Table 1). Interestingly, the best percent conversions were observed for

---

Keywords: Montmorillonite K10 clay; Hetero-Diels–Alder; Dienes; Benzaldehydes; Chelation; Dihydropyran; Green chemistry.

* Corresponding author. Tel.: +1 773 325 4726; fax: +1 773 325 7421; e-mail: mdintzne@depaul.edu

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.01.010

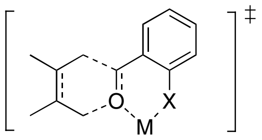
Table 1. Reaction scope

Entry	Aldehyde	Time (min)	Product[4]	% Conversion[a]
1	Benzaldehyde (**2a**)	60	**3a**	52
2	*o*-Anisaldehyde (**2b**)	60	**3b**	81
3	*o*-Ethoxybenzaldehyde (**2c**)	60	**3c**	25
4	*o*-Fluorobenzaldehyde (**2d**)	15	**3d**	49
5	*o*-Chlorobenzaldehyde (**2e**)	60	**3e**	34
6	*o*-Bromobenzaldehyde (**2f**)	60	**3f**	68
7	*o*-Cyanobenzaldehyde (**2g**)	24	**3g**	22
8	*o*-Nitrobenzaldehyde (**2h**)	60	**3h**	75
9	*o*-Tolualdehyde (**2i**)	60	**3i**	7
10	*p*-Anisaldehyde (**2j**)	60	**3j**	<1
11	*p*-Chlorobenzaldehyde (**2k**)	24	**3k**	56
12	*p*-Nitrobenzaldehyde (**2l**)	24	**3l**	56

[a] Measured by GC–MS.

benzaldehyde derivatives with electronegative substituents in the *ortho* position, in particular *o*-anisaldehyde, which we surmise allows for transition-state stabilization involving possible chelation of the clay's metal ions with aldehyde oxygen (**4**, Fig. 1). Apparently, the stabilizing interaction of the aldehyde's *ortho*-substituent with the clay compensates for electronic deactivation, especially with substrates like **2b**, for which hetero-Diels–Alder reactions have until now been absent from the literature. Minimal Diels–Alder reaction observed with *o*-tolualdehyde (**2i**), for which chelation is not possible, further supports our proposal for possible transition-state stabilization via coordination of the clay with the aldehyde oxygen and electron-rich *ortho*-substituents.

In order to further optimize the desired reaction, we next investigated the effect of the relative amount of clay used on the hetero-Diels–Alder reaction of *o*-anisaldehyde (**2b**) with 2,3-dimethy-1,3-butadiene (**1**). The reaction was run with increasing amounts of clay and a sharp increase in percent conversion to **3b** was observed with 1.4–2.0 mass equiv of clay relative to aldehyde (Table 2 and Fig. 2). Thus, the reaction appeared to work best



4

M = Activated Montmorillonite K10

X = $-OCH_3$, -F, -Cl, -Br, OCH_2CH_3

Figure 1. Proposed hetero-Diels–Alder transition state.

Table 2. Clay titration

Entry	Relative amount of clay by mass	% Conversion[a]
1	0.2	10
2	0.4	23
3	1.0	14
4	1.2	34
5	1.4	73
6	1.6	72
7	1.8	79
8	2.0	81

[a] Measured by GC–MS.

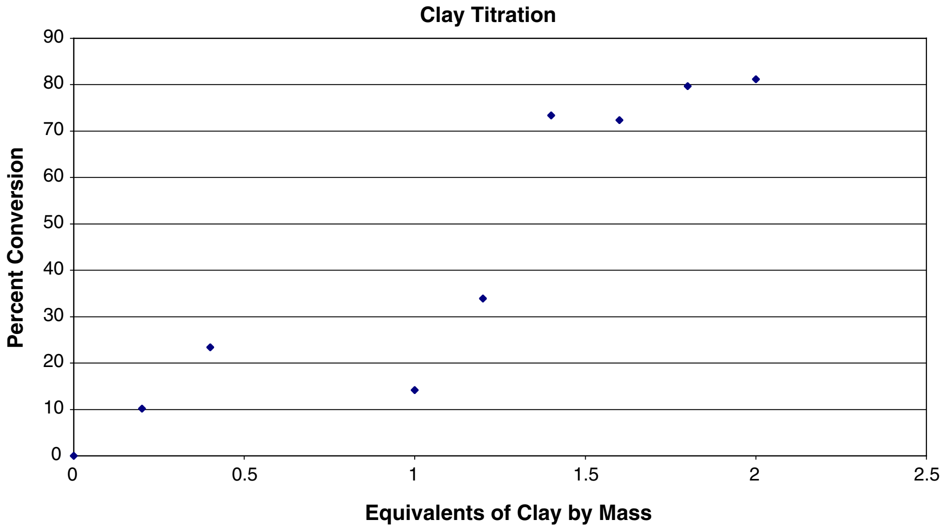
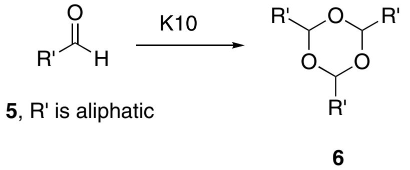


Figure 2. Clay titration.



Scheme 2. Clay-catalyzed trimerization of aliphatic aldehydes.

with clay that was activated at 200 °C for 1 h and used in twofold mass excess relative to the aldehyde.

Attempts to carry out similar reactions with less substituted dienes, such as isoprene, were only minimally successful, giving some of the desired Diels–Alder adducts but larger amounts of products of higher molecular weights. The use of aliphatic aldehydes, such as propionaldehyde and butyraldehyde (**5**, Scheme 2), as the dienophile component resulted not in the formation of the Diels–Alder adducts, but gave predominantly the corresponding trioxane products (**6**). We are currently investigating the clay-catalyzed trimerization of aliphatic aldehydes, which will be reported in a separate Letter.

As 'green chemistry' becomes more prevalent in organic synthesis,[8–14] environmentally benign clays are becoming attractive alternatives to more toxic Lewis acid catalysts for an array of reactions,[15,16] and optimization of conditions for their use is necessary. The work reported here has proven important in our ongoing efforts to demonstrate the utility of Montmorillonite clays in organic synthesis, and may prove useful for others as well. We are currently investigating the additional applications of clays as catalysts for organic reactions.

A representative experimental procedure for the clay-catalyzed hetero-Diels–Alder follows for **3b**: Montmorillonite K10 clay (50 mg) was measured into a vial and heated in an oven at approximately 200 °C for 1 h. The activated clay was transferred to a desiccator and allowed to cool to room temperature. To the clay was added 0.1 mL CCl_4, followed by 0.11 mmol *o*-anisaldehyde. The mixture was allowed to sit for about 5 min. Then, 2,3-dimethyl-1,3-butadiene (0.10 mmol) was added via pipette. The reaction mixture was allowed to sit at room temperature for 1 h, then filtered to remove the clay. Solvent was removed under vacuum and the product isolated as a pale yellow oil (15 mg, 94% based on the recovered starting material) and analyzed by IR and NMR spectroscopy and GC–MS.[17]

Acknowledgments

We thank DePaul University's College of Liberal Arts and Science funding, and the National Science Foundation CCLI A&I program (Grant No. DUE-0310624) for the support in purchasing our Bruker Avance 300 MHz NMR spectrometer.

References and notes

1. Review: Bednarski, M. D.; Lyssikatos, J. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 2, pp 661–706.
2. Review: Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987.
3. Review: Danishefsky, S. J.; Deninno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15–23.
4. Oi, S.; Kashiwagi, K.; Terada, E.; Ohuchi, K.; Inoue, Y. *Tetrahedron Lett.* **1996**, *37*, 6351–6354.
5. Dintzner, M. R.; McClelland, K. M.; Morse, K. M.; Akroush, M. H. *Synlett* **2004**, *11*, 2028–2030.
6. Dintzner, M. R.; Lyons, T. W.; Akroush, M. H.; Wucka, P.; Rzepka, A. T. *Synlett* **2005**, *5*, 785–788.
7. Yahiaoui, A.; Belbachir, M.; Hachemaoui, A. *Int. J. Mol. Sci.* **2003**, *4*, 548–561.
8. Zhao, H.; Malhotra, S. V. *Aldrichim. Acta* **2002**, *35*, 75–83.
9. Li, M.; Xu, Z.; Ma, C.; Zhang, W. *Zhejiang Gongye Daxue Xuebao* **2002**, *30*, 500–504.
10. Tundo, P.; Perosa, A. *Chem. Rev.* **2002**, *2*, 13–23.
11. Onaka, M. *Gendai Kagaku* **2002**, *371*, 14–20.
12. Onaka, M. *Petrotech* **2001**, *24*, 837–841.
13. Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Chem. Commun.* **2001**, *21*, 2159–2169.
14. Reed, S. M.; Hutchinson, J. E. *J. Chem. Ed.* **2000**, *77*, 1627–1629.
15. Nagendrappa, G. *Resonance* **2002**, 64–77.
16. Corey, E. J.; Wu, L. I. *J. Am. Chem. Soc.* **1993**, *115*, 9327–9328.
17. *3,6-Dihydro-4,5-dimethyl-2-(2-methoxyphenyl)-2H-pyran* (**3b**). IR: 2918, 2835, 1589, 1493, 1462, 1371, 1287, 1242, 1100, 1050, 1032, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.63 (d, $J = 7.6$ Hz, 1H), 7.32 (t, $J = 7.8$ Hz, 1H), 7.09 (t, $J = 7.5$ Hz, 1H), 6.92 (d, $J = 8.1$ Hz, 1H), 5.04 (dd, $J =$ 3.8, 8.2 Hz, 1H), 4.27 (m, 2H), 3.87 (s, 3H), 2.30 (m, 2H), 1.79 (s, 3H), 1.70 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.8, 136.5, 128.1, 126.1, 124.3, 120.9, 110.1, 70.9, 70.5, 55.2, 37.6, 18.4, 13.9 ppm; GC–MS (70 eV), $t_R = 11.612$ min, m/z 218 M^+ (44%); 135, $[M-83]^+$ (100%); 82, $[M-136]^+$ (79%); 67, $[M-151]^+$ (87%).