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Tetrahedron Letters 46 (2005) 555-558

Tetrahedron Letters

Remarkable effects of titanium tetrachloride in diastereoselective aza Diels–Alder cycloaddition: synthesis of (S)-piperazic acid

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Received 28 October 2004; revised 26 November 2004; accepted 1 December 2004

Abstract—Titanium tetrachloride-mediated aza Diels–Alder cycloaddition using a chiral diene and an aza dienophile proceeds in highly diastereoselective manner to form a dehydropiperazic acid derivative in high yield, and diastereoselectivity of the reaction depends on the quantity of titanium tetrachloride. © 2004 Published by Elsevier Ltd.

1. Introduction

Asymmetric hetero Diels–Alder reaction is one of the versatile reactions for access to heterocycles, which constitute the structural skeleton of a large number of natural products.¹ In our continuing synthetic studies² on biologically interesting cyclodepsipeptides, GE3 and polyoxypeptins bearing piperazic acid,^{3,4} we focused on aza Diels–Alder reaction⁵ utilizing aza dienophile **3** and chirally modified diene **4** as a key step, which is obviously a simple and straightforward way for preparation of piperazic acid (Fig. 1). In addition, Diels–Alder adduct **5** can be transformed to not only piperazic acid (**1**) but also 5hydroxypiperazic acid (**2**), a novel component of polyoxypeptin A. In the course of the study, we found remarkable effects of titanium tetrachloride on the diastereoselectivity of asymmetric aza Diels–Alder cycloaddition. Herein we report a highly diastereoselective synthesis of (*S*)-piperazic acid by titanium tetrachloride-mediated aza Diels– Alder cycloaddition using a chiral diene and an aza dienophile. As a related work, Stoodley and co-workers has already reported an aza Diels–Alder approach for construction of dehydropiperazic acid derivatives by employment of a very different strategy.^{5c,e}

2. Results and discussion

In the aza Diels–Alder strategy utilizing a chiral diene we chose a 2,4-pentadienoic acid derivative with Evans'



Figure 1. Synthetic plan for piperazic acids and 5-hydroxypiperazic acids.

Keywords: Piperazic acid; Titanium chloride; Aza Diels-Alder cycloaddition; Chiral diene.

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Scheme 1.

chiral 2-oxazolidinone, which was readily prepared as illustrated in Scheme 1. Reaction of pent-2,4-die-

Table 1. Lewis acid effects on diastereoselective aza Diels-Alder reaction^a

noic acid with pivaloyl chloride in the presence of triethylamine followed by lithium salt 6 of Evans' chiral oxazolidinone provided oxygen- and light-sensitive chiral diene 4 in 76% yield.

With the chiral diene available, we examined the aza Diels–Alder reaction and the results are summarized in Table 1. 4-Phenyltriazoline-3,5-dione (8, PTAD), an aza dienophile, was in situ generated by oxidation of 4-phenylurazole (7) with *tert*-butylhypochlorite (1 equiv) at 23 °C for 2 h and used without further purification.⁶ In preliminary experiments using the chiral



Entry	Lewis acid (equiv)	Conditions	Isolated yield ^b (%)	Diastereomeric ratio ^c
1 ^d	AlCl ₃	-78 °C to rt, 18 h	100	50:50
2		-78 °C to rt, 21 h	61	53:47
3	TiCl ₄ (1 equiv)	-78 °C to rt, 21 h	46	83:17
4	$TiCl_4$ (0.5 equiv)	−78 °C to rt, 17 h	83	84:16
5	TiCl ₄ (2 equiv)	−78 °C to rt, 17 h	100	84:16
6	TiCl ₄ (3 equiv)	−78 °C to rt, 17 h	95	97:3
7	TiCl ₄ (4 equiv)	-78 °C to rt, 17 h	57	96:4

^a The reaction was carried out by using PTAD (1 equiv), chiral diene (1 equiv), Lewis acid in methylene chloride. PTAD was generated in situ by reaction of phenylurazole (1 equiv) with *tert*-butylhypochloride (1 equiv) at 23 °C for 1 h.

^b Yield of **9a** and **9b**.

^c Determined by ¹H NMR analysis of the crude product.

^d The reaction was carried out by using the chiral diene with L-menthol as a chiral auxiliary instead of Evans' imide. In the case of $TiCl_4$. Yb(OTf)₃ or FeCl₃ as a Lewis acid, the reaction gave the same results as that of AlCl₃.



Scheme 2. Synthesis of (*S*)-piperazic acid. Reagents and conditions: (a) *t*-BuOCl, CH_2Cl_2 , 0 °C to rt, 2 h; (b) $TiCl_4$ (3 equiv), CH_2Cl_2 , -78 °C to rt, 17 h, 95% (97:3); (c) H_2 , 5% Pd–C, THF, rt, 15 h, 94%; (d) LiBH₄, THF, H_2O , 0 °C, 6 h, 95%; (e) KOH, *n*-BuOH, relux, 20 h, 77%; (f) CbzCl, NaHCO₃, ether, H_2O 64%; (g) TEMPO, NaClO–NaClO₂, CH_3CN , phosphate buffer (pH 6.8), 91%; (h) H_2 , 5% Pd–C, CH_2Cl_2 , trifluoroacetic acid, 99%.

diene bearing L-menthol ester as a chiral auxiliary, the reaction was found to proceed almost quantitatively to give the adducts but with no diastereoselectivity even in the presence of various Lewis acids (entry 1). To overcome this problem, we chose titanium tetrachloride as a Lewis acid and bidentate diene 4 with the chiral oxazolidinone, and explored the Lewis acid effects in aza Diels-Alder reaction of 4 with 8. As anticipated, noncatalyzed Diels-Alder reaction gave a diastereomeric mixture of adducts 9a and 9b in moderate yield with no diastereoselectivity. The presence of 1 equiv of titanium tetrachloride, however, showed a good level of diastereoselection (83:17) in moderate yield (46%, entry 3). Although the stereochemistry of the major product remained unclear, it was unambiguously confirmed after conversion to the final piperazic acid. After extensive optimization of the reaction conditions, we found remarkable Lewis acid effects in that an increased amount of titanium tetrachloride affects the diastereoselectivity favorably. With 0.5-2 equiv of titanium tetrachloride, the same levels of diastereoface selectivities were observed (entry 3-5).⁷ On the other hand, in the presence of 3 equiv of titanium tetrachloride (entry 6),

the diastereoselectivity dramatically increased (97:3) and the cycloadduct **9a**, $[\alpha]_D^{23} - 20.3$ (*c* 1.41, CHCl₃), was obtained in 95% isolated yield. It is interesting that the aza Diels–Alder reaction using an increased amount of Lewis acid not only proceeds in high diastereoselectivity but also almost quantitative yield. The use of a larger amount of titanium tetrachloride (>4 equiv) still gave high diastereoselectivity (96:4) but caused decreased yield (57%) (entry 7). Nonetheless, the above results are noteworthy because the reaction is a successful, rare example of a highly diastereoselective aza Diels–Alder cycloaddition using the chiral diene and demonstrates the novel phenomenon that the diastereoselectivity and the yield depend on the quantity of titanium tetrachloride.

The facial selectivity and the requirement of 3 equiv of titanium tetrachloride (Table 1) in the aza Diels–Alder cycloaddition can be rationalized as follows (Fig. 2). In the case of the noncatalyzed reaction, the four conformers (A–D) of the chiral diene are present, and among them, the predominant conformers are A and **B** for preventing severe interaction by the $A^{1,3}$ strain



Figure 2. Noncatalyzed aza Diels-Alder reaction and Lewis acid-catalyzed Diels-Alder reaction.

on the C–N bond between the diene carboxylic acid residue and chiral oxazolidinone, which should equally react with dienophile **8** to afford **9a** and **9b**, respectively. In titanium tetrachloride-mediated reaction, 1 equiv of the Lewis acid serves as the chelator between the two carbonyl functions in the chiral diene and the presence of the chelation causes production of two limited conformers **E** and **F** to be produced. The conformer **E** should be dominant in the absence of the $A^{1,3}$ strain and reacts with the dienophile activated by the remained 2 equiv of titanium chloride at the *si*-face in *endo*-selective manner to furnish predominantly **9a**.

With cycloadduct **9a** in hand, we investigated synthesis of piperazic acid (Scheme 2). Hydrogenation of 9a provided protected piperazic acid 10 in 94% yield. Unfortunately, the direct conversion of 10 to piperazic acid failed due to insolubility of **10** in reaction media. Several attempts to obtain 1 under acidic conditions were in vain. Therefore, we had to employ an indirect route to 1. Reductive removal of the chiral auxiliary using lithium borohydride to generate alcohol 11 and following alkaline hydrolysis using potassium hydroxide in *n*-butanol under refluxing conditions gave pyridazinemethanol 12 in good overall yield.5b Protection of two nitrogens with benzyloxycarbonyl chloride to form alcohol 13, $[\alpha]_{D}^{22}$ +12.6 (c 1.03 CHCl₃), and subsequent oxidation with sodium hypochlorite-sodium chlorite in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)⁸ in acetonitrile-phosphate buffer (pH 6.8) afforded di-Cbz-piperazic acid (14), $[\alpha]_D^{23}$ -19.6 (c 1.04 CHCl₃), in 90% yield and in two steps. Final deprotection of 14 in the presence of trifluoroacetic acid in methylene chloride furnished piperazic acid trifluoroacetate $(1)^9$ in 30% overall yield from readily available pent-2,4-dienoic acid. The absolute configuration of 1 was unambiguously established to be S after its conversion to the DNP derivative by its chiral HPLC analysis.¹⁰

In conclusion, we have developed a highly diastereoselective aza Diels–Alder cycloaddition using a chiral diene, in which the diastereoselectivity depends on the quantity of titanium tetrachloride. The facial selectivity in the aza Diels–Alder cycloaddition can be explained in terms of the $A^{1,3}$ strain and the chelation control by titanium tetrachloride. The obtained cycloadduct was efficiently transformed to medicinally important piperazic acid in 30% overall yield.

Acknowledgements

This work was financially supported in part by a Grantin-Aid for Scientific Research (B) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

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- 6. *t*-BuOCl is completely consumed with quantitative production of PTAD (see Table 1, entry 5).
- 7. In the case of 1 equiv of TiCl₄, the starting diene unexpectedly remained in the reaction, and therefore the yield was moderate.
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- 9. (*S*)-1 Trifluoroacetate: mp 149–151 °C (ethyl acetate/ ethanol); $[\alpha]_{22}^{22}$ +11.1 (*c* 0.98, MeOH); IR (KBr) 3292, 3080, 2967, 2922, 2836, 2760, 1720, 1664, 1589, 1509, 1421, 1232, 1198, 1183, 1130, 1082, 916, 842, 801, 725 cm⁻¹; ¹H NMR (400 MHz, D₂O): δ 1.85–1.95 (m, 3H), 2.13–2.18 (m, 1H), 3.14–3.21 (m, 1H), 3.27 (m, 1H), 3.89 (m, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 20.22, 24.91, 43.99, 55.86, 117.12 (q, *J* = 297.8 Hz), 158.47 (q, *J* = 31.3 Hz), 171.52. Anal. Calcd for C₇H₁₁F₃N₂O₄: C, 34.43; H, 4.54; N, 11.47. Found: C, 34.32; H, 4.46; N, 11.38.
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