Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 47 (2006) 1537–1539
Tetrahedron Letters

A convenient and versatile approach to 2,3-dihydro-4*H*-pyran-4-ones via tandem aldol reaction-conjugate addition

Bo Gao,[a] Zhipeng Yu,[a] Zhengyan Fu[a] and Xiaoming Feng[a,b,*]

[a]*Key Laboratory of Green Chemistry and Technology (Sichuan University), Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China*
[b]*State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, China*

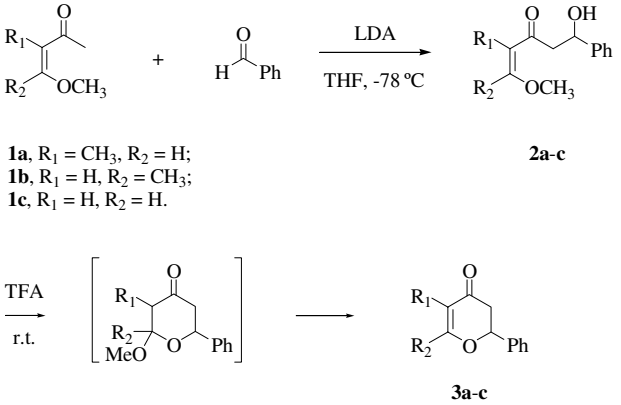
Received 21 November 2005; revised 4 January 2006; accepted 4 January 2006

Abstract—Aldol reaction of enones **1a–c** with aldehydes followed by intramolecular conjugate addition proceeded smoothly to afford corresponding 2,3-dihydro-4*H*-pyran-4-ones in high yields under mild conditions.

2,3-Dihydro-4*H*-pyran-4-ones are highly versatile synthetic intermediates for the preparation of biologically important compounds,[1] such as carbohydrates,[1a–c] antibiotics,[1d] and toxins.[1e–g] These compounds used to be prepared using hetero-Diels–Alder reaction of carbonyl compounds with Danishefsky's dienes[2] and other activated dienes[3] in the last two decades. Recently, Gouverneur's group reported a novel entry to 2,3-dihydro-4*H*-pyran-4-ones by oxidative cyclization of β-hydroxyenones with Palladium(II).[4] However, the reaction did not tolerate the presence of a substituent on the vinylic carbon adjacent to the carbonyl group, which prevented the formation of 2,5-disubstituted 2,3-dihydro-4*H*-pyran-4-ones. More recently, Winkler's group disclosed a one-step synthesis of 2,6-disubstituted 2,3-dihydro-4*H*-pyran-4-ones from β-ethoxy α,β-unsaturated lactones.[5]

Although the hetero-Diels–Alder reaction of Danishefsky's dienes provides one of the most convenient approaches to this ring system,[2] the preparation and purification of Danishefsky's dienes are found to be troublesome.[6] It would be synthetically useful if Danishefsky's dienes were replaced by easily available and stable materials. Accordingly, we wish to develop an alternative protocol to synthesize these heterocycles from enones **1a–c**,[7] the key materials for the preparation of Danishefsky's dienes (Scheme 1). The intermediates **2a–c** of these reactions were isolated and assigned as aldol adducts by ^{1}H NMR analysis.[8] They were then completely converted into the desired products **3a–c** through intramolecular conjugate addition.

Our studies were started with the reaction of enone **1a**, LDA, and benzaldehyde. Enone **1a** (45 μL, 0.375 mmol) was added via syringe to a THF solution of LDA (2 M in THF/*n*-heptane) under nitrogen atmosphere for the formation of lithium enolate firstly.[9] After 20 min, benzaldehyde (26 μL, 0.25 mmol) was added, followed by stirring at the same temperature for 24 h. Then the reaction was quenched with sat. NH_4Cl (aq) and treated with TFA (200 μL) in the same pot for 2 h at ambient temperature to yield 5-methyl-2-phenyl-2,3-dihydro-4*H*-pyran-4-one **3a**. The effects of LDA



1a, $R_1 = CH_3$, $R_2 = H$;
1b, $R_1 = H$, $R_2 = CH_3$;
1c, $R_1 = H$, $R_2 = H$.

2a-c

3a-c

Scheme 1.

* Corresponding author. Tel./fax: +86 28 8541 8249; e-mail: xmfeng@scu.edu.cn

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.01.010

loading, benzaldehyde concentration, and reaction temperature were studied. When 0.8 equiv of LDA was used, 43% yield was obtained (entry 1). Increasing LDA loading to 1.6 equiv resulted in higher yields (entries 2 and 3). When 3.0 equiv of LDA was used, yield was decreased significantly (entry 4). Then, 1.6 equiv of LDA was chosen as optimum loading. When the concentration of benzaldehyde was lowered from 0.5 to 0.25 M, the yield was somewhat sacrificed (entry 5 vs 3). Encouragingly, 94% isolated yield was achieved when the concentration of benzaldehyde was increased to 1.0 M (entry 6). Further increase of the concentration to 1.25 M led to less satisfying yield (entry 7). Studies on the temperature effect revealed that −78 °C was the optimum temperature for this reaction. Raising the reaction temperature to −45 °C led to lower yield (entry 8). It was noteworthy that when the temperature was elevated to above −10 °C, only trace amount of the product was observed (entries 9 and 10) (Table 1).

With these results in hand, we decided to explore the generality of this protocol. Firstly, a variety of aromatic and aliphatic aldehydes were subjected to the reaction with enone **1a**. As shown in Table 2, substituted benzaldehyde, both electron-donating groups and electron-withdrawing groups, could give good yields (entries 2–12). Fused aromatic aldehyde (entry 13) and hetero-aromatic aldehyde (entry 14) also gave high yields. More significant examples were the reactions of (*E*)-3-phenyl-2-propenal (entry 15) and *n*-hexanal (entry 16), which reacted with enone **1a** in much higher yields than with activated diene.[6b] Cyclohexanecarbaldehyde (entry 17), which is more hindered at alpha position than *n*-hexanal (entry 16) also gave good yield as the latter did. Then, enones **1b** and **1c** were chosen to examine the tolerance of substitutes on enones. The reaction of enone **1b** with benzaldehyde proceeded smoothly to give rise to the desired product in 93% yield (entry 18). However, enone **1c** was reacted with benzaldehyde in poor yield (entry 19).

In conclusion, the present work has shown that the approach can be used for the synthesis of structurally diversed disubstituted dihydropyrones in high yields. An attractive feature of this method is the possibility to obtain these heterocycles from simple substrates, avoiding thus the use of activated dienes possessing one or two oxygen-containing donating groups. Further work is in progress to develop enantioselective version of this transformation.

Table 1. Optimization studies

Entry	LDA Loading (equiv)[a]	Benzaldehyde concn (M)	Temp (°C)	Yield (%)[b]
1	0.8	0.5	−78	43
2	1.0	0.5	−78	69
3	1.6	0.5	−78	78
4	3.0	0.5	−78	26
5	1.6	0.25	−78	68
6	1.6	1.0	−78	94
7	1.6	1.25	−78	84
8	1.6	1.0	−45	72
9	1.6	1.0	−10	Trace
10	1.6	1.0	0	Trace

[a] Based on benzaldehyde.
[b] Isolated yield.

Table 2. Tandem aldol reaction-conjugate addition of enones **1a–c** with aldehydes[a]

Entry	Enone	Aldehyde	Yield (%)[b]
1	**1a**	Benzaldehyde	94
2	**1a**	2-Methylbenzaldehyde	81
3	**1a**	3-Methylbenzaldehyde	85
4	**1a**	4-Methylbenzaldehyde	92
5	**1a**	2-Chlorobenzaldehyde	95
6	**1a**	3-Chlorobenzaldehyde	83
7	**1a**	4-Chlorobenzaldehyde	86
8	**1a**	2-Nitrobenzaldehyde	80
9	**1a**	3-Nitrobenzaldehyde	81
10	**1a**	3-Methoxybenzaldehyde	84
11	**1a**	4-Methoxybenzaldehyde	87
12	**1a**	4-Fluorobenzaldehyde	91
13	**1a**	1-Naphthaldehyde	83
14	**1a**	2-Furaldehyde	87
15	**1a**	(*E*)-3-Phenyl-2-propenal	81
16	**1a**	*n*-Hexanal	75
17	**1a**	Cyclohexanecarbaldehyde	76
18	**1b**	Benzaldehyde	93
19	**1c**	Benzaldehyde	58

[a] All reactions were carried out in THF with 1.5 equiv of enones **1a–c** and 1.6 equiv of LDA at −78 °C as detail in the typical experimental procedure.[10]
[b] Isolated yield based on aldehyde.

Acknowledgments

The authors thank the National Natural Science Foundation of China (Nos. 20225206, 20390055, and 20472056) and the Ministry of Education of China (Nos. 20030610021 and 104209) for financial support.

References and notes

1. For examples, see: (a) Danishefsky, S. J.; Pearson, W. H.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 1280–1285; (b) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15–23; (c) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed.* **1996**, *35*, 1380–1419; (d) Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.* **1988**, *110*, 4368–4378; (e) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *Org. Lett.* **2000**, *2*, 231–234; (f) Cox, J. M.; Rainier, J. D. *Org. Lett.* **2001**, *3*, 2919–2922; (g) Yamashita, Y.; Saito, S.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3793–3798; (h) Williams, D. R.; Heidebrecht, R. W., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 1843–1850.
2. (a) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558–3588; (b) Jørgensen, K. A. *Eur. J. Org. Chem.* **2004**, 2093–2102.
3. (a) Barluenga, J.; Aznar, F.; Fernández, M. *Tetrahedron Lett.* **1995**, *36*, 6551–6554; (b) Evans, P. A.; Nelson, J. D. *J. Org. Chem.* **1996**, *61*, 7600–7602; (c) Evans, P. A.; Nelson, J. D.; Manangan, T. *Synlett* **1997**, 968–970; (d) Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 9662–9663.

4. Reiter, M.; Ropp, S.; Gouverneur, V. *Org. Lett.* **2004**, *6*, 91–94.
5. Winkler, J. D.; Oh, K. *Org. Lett.* **2005**, *7*, 2421–2423.
6. (a) Wang, B.; Feng, X.-M.; Cui, X.; Liu, H.; Jiang, Y.-Z. *Chem. Commun.* **2000**, 1605–1606; (b) Huang, Y.-Z.; Feng, X.-M.; Wang, B.; Zhang, G.-L.; Jiang, Y.-Z. *Synlett* **2002**, 2122–2124; (c) Fu, Z.-Y.; Gao, B.; Yu, Z.-P.; Yu, L.; Huang, Y.-Z.; Feng, X.-M.; Zhang, G.-L. *Synlett* **2004**, 1772–1775; (d) Gao, B.; Fu, Z.-Y.; Yu, Z.-P.; Yu, L.; Huang, Y.-Z.; Feng, X.-M. *Tetrahedron* **2005**, *61*, 5822–5830.
7. Enone **1a** was prepared according to the reported procedure: (a) Miyashita, M.; Yamasaki, T.; Shiratani, T.; Hatakeyama, S.; Miyazawa, M.; Irie, H. *Chem. Commun.* **1997**, 1787; (b) see Ref. 6c; Enone **1b** was prepared according to the reported procedure: (c) Smissman, E. E.; Voldeng, A. N. *J. Org. Chem.* **1964**, *29*, 3161–3165. Enone **1c** was prepared according to the same procedure as for **1a**.
8. ^{1}H NMR data of compounds **2a–c**: Compound **2a**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.41$–7.20 (m, 6H, Ph–H and =CH), 5.20–5.17 (m, 1H, Ph–CHO), 3.96 (d, 1H, $J = 2.4$ Hz, OH), 3.84 (s, 3H, OCH_3), 2.94–2.83 (m, 2H, CH_2), 1.72 (s, 3H, =C—CH_3). Compound **2b**: ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.24$–7.11 (m, 5H, Ph–H), 5.26 (s, 1H, =CH), 5.03 (m, 1H, Ph–CHO), 3.89 (d, 1H, $J = 2.2$ Hz, OH), 3.49 (s, 3H, OCH_3), 2.68 (d, 2H, $J = 6.1$ Hz, CH_2), 2.19 (s, 3H, =C—CH_3). Compound **2c**: ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.63$ (d, 1H, $J = 12.7$ Hz, =CHO), 7.40–7.34 (m, 5H, Ph–H), 5.59 (d, 1H, $J = 12.7$ Hz, =CH), 5.20–5.18 (m, 1H, Ph–CH), 3.72 (s, 3H, OCH_3), 3.79 (s, 1H, OH), 2.87–2.86 (m, 2H, CH_2).
9. LDA is one of the most important and convenient Bronsted bases for the enolization of α,β-unsaturated carbonyl compounds. For examples, (a) Stork, G.; Kraus, G. A. *J. Am. Chem. Soc.* **1976**, *98*, 2351–2352; (b) Faller, J. W.; Smart, C. J. *Tetrahedron Lett.* **1979**, *20*, 4911–4914; (c) Clive, D. L. J.; Bergstra, R. J. *J. Org. Chem.* **1991**, *56*, 4976–4977; (d) see Refs. 6b, 6c, and 7a.
10. A typical experimental procedure is given for the synthesis of 5-methyl-2-phenyl-2,3-dihydro-4*H*-pyran-4-one **3a**: To a solution of LDA (200 μL, 2 M in THF/*n*-heptane, 0.4 mmol) in THF (0.25 mL) was added enone **1a** (45 μL, 0.375 mmol) via syringe at −78 °C under nitrogen atmosphere. After the mixture was stirred for 20 min, benzaldehyde (26 μL, 0.25 mmol) was added. The reaction was allowed to stir at −78 °C for 24 h, after which it was quenched with sat. NH_4Cl (aq) and treated with TFA (200 μL). After stirring for 2 h at ambient temperature, the reaction was quenched with sat. $NaHCO_3$ (aq) and extracted with ether (4×5 mL). The organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (petroleum ether–ether, 9:1) to yield 5-methyl-2-phenyl-2,3-dihydro-4*H*-pyran-4-one (44 mg, 94% yield), white solid, mp = 46–48 °C. ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.46$–7.40 (m, 5H, Ph–H), 7.39 (s, 1H, =CH), 5.41 (dd, ^3J(H,H) = 14.6, 3.2 Hz, 1H, Ph–CHO), 2.94–2.88 (m, 1H, CH_AH_B), 2.73–2.69 (m, 1H, CH_AH_B), 1.76 (s, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 192.59$, 159.49, 138.27, 128.80, 128.78, 126.05, 114.14, 80.99, 43.21, 10.51.