Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 3797–3799
Tetrahedron Letters

Liquid-phase parallel synthesis of 2-aryl-5-methoxyl-carbonyl-dihydropyrones using soluble polymer support

Jun-Ke Wang,* Ying-Xiao Zong, Hong-Gang An, Guo-Qing Xue, Dong-Qing Wu and Yong-Sheng Wang

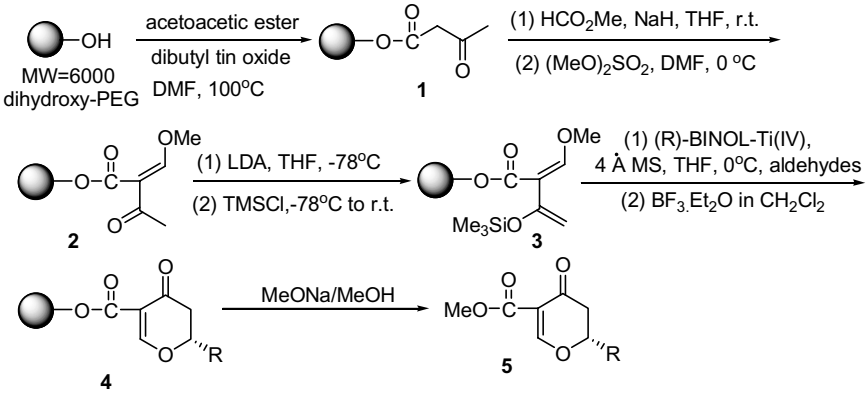
Key Laboratory of Resources and Environment Chemistry of West China, Department of Chemistry, Hexi University, Zhangye 734000, PR China

Received 6 March 2005; revised 29 March 2005; accepted 30 March 2005
Available online 12 April 2005

Abstract—General and efficient methods for the construction of 2-aryl-5-methoxylcarbonyl-dihydropyrones on soluble polymer support have been developed. The hetero-Diels–Alder reaction of aldehydes with poly(ethylene glycol) (PEG)-bound Danishefsky's diene derived from PEG-bound acetoacetate, followed by cleavage from the support, afforded 2-aryl-5-methoxylcarbonyl-dihydropyrones. The products were obtained in good yields and high enantioselectivities.

Recently, organic synthesis of small molecular compounds on soluble polymers (i.e., liquid-phase synthesis) has been the focus of intense research activity.[1] It couples the advantages of homogeneous solution chemistry (high reactivity, lack of diffusion phenomena, and ease of analysis without the cleavage-and-check procedure) with those of solid-phase chemistry (use of excessive reagents and easy isolation and purification of product). Among the various soluble polymers, poly(ethylene glycol) (PEG) is the most useful and promising.[2]

Hetero-Diels–Alder reactions of activated dienes (such as Danishefsky's diene) with aldehydes or ketones are very important in the formation of optically active dihydropyrones. Many researches were carried out focusing mostly on looking for the asymmetric catalysis to improve yields and enantioselectivities.[3–6] Chiral 2,5-disubstituted dihydropyrone derivatives have been prepared in solution by Danishefsky et al. using the chiral auxiliary–chiral catalyst combination strategy.[7] In connection with our research on the PEG-supported



Scheme 1.

Keywords: Poly(ethylene glycol) (PEG); Dihydropyrones; Danishefsky's diene; Hetero-Diels–Alder reaction; Liquid-phase synthesis.
* Corresponding author. Tel.: +86 93 6828 4286; fax: +86 93 6828 2045; e-mail addresses: wangjk@hxu.edu.cn; wjkzyx@sohu.com

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.03.192

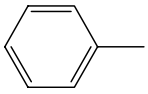
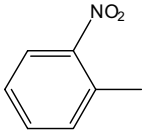
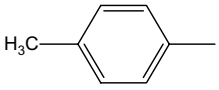
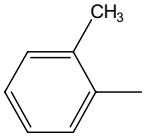
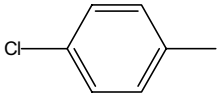
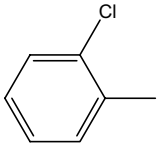
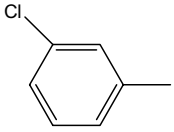
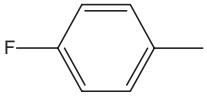
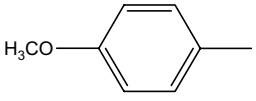
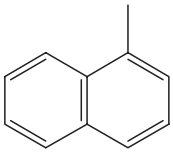
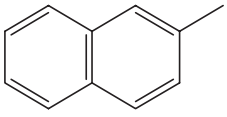
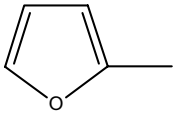
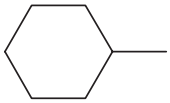
liquid-phase synthesis,[8] herein, we wish to report preliminarily the parallel synthesis of 2-aryl-5-methoxylcarbonyl-dihydropyrones through a hetero-Diels–Alder reaction of aldehydes with PEG-bound activated dienes using chiral BINOL–Ti(IV) complex on PEG support.

As described in Scheme 1, the commercially available acetoacetic ester was attached to the PEG6000 support by transesterification of PEG with acetoacetic ester in the presence of dibutyl tin oxide in anhydrous DMF at 100 °C. The conversion of terminal hydroxyl groups on PEG was determined by IR and ^{1}H NMR analysis to be quantitative. According to the literature,[9] the PEG-bound **1** was treated with NaH and methyl formate in THF at −10 °C, then treated, after the solvent was replaced by DMF, with dimethyl sulfate to afford PEG-bound **2** to which were added LDA and TMSCl to yield PEG-bound diene **3**. PEG-bound diene **3** reacted with aldehyde in the presence of the mixture of (*R*)-BINOL, Ti(*i*-PrO)$_4$ (1 M in toluene), and activated powdered 4 Å MS in toluene at 0 °C for 48 h followed by addition of $BF_3 \cdot Et_2O$ in CH_2Cl_2 to give PEG-bound **4**. We examined several different catalysts including chiral BINOL–Ti(IV) complex, the tryptophan-derived oxazaborolidine catalysis, bisoxazoline-derived chiral catalysts, the chiral activators for the titanium(IV) catalysis, tridentate Schiff base chromium(III) complexes, as well as chiral pyrrolidines catalysis, and found that chiral BINOL–Ti(IV) complex gave good to excellent yields and high enantioselectivities for the reaction of PEG-bound Danishefsky's diene **3** with representative aldehydes. Moreover, after many examinations being conducted, we found that solvents have much influence on the enantioselectivities and that THF is the best solvent in enantioselectivities. This result is consistent with the literature[10] and may result from THF changing the structure of this catalyst. Compounds **1**–**4** were purified by precipitation and washing with diethyl ether. The whole course of the reaction was estimated directly by IR and ^{1}H NMR without detaching material from the PEG support. PEG-bound **4** efficiently cleaved from the support with MeONa/MeOH at room temperature for about 5 h to provide the desired compounds **5**.[11]

A variety of aldehydes were examined, and all compounds provided satisfactory NMR and MS spectra.[12] As indicated in Table 1, the yields are good to excellent (73–99%) and the purities are satisfactory (85–96%). In order to extend the scope of the applications of PEG-bound diene **3**, the reaction of the PEG-bound diene **3** with ketones and imines is proceeding.

In conclusion, we herein show soluble polymer supported methodology for the efficient parallel synthesis of 2-aryl-5-methoxylcarbonyl-dihydropyrones. Due to the homogeneity of the reactions on PEG support, products were obtained in good yields and high enantioselectivities. All reactions involved here are highly efficient in giving the desired compound. Crude products are usually obtained in high purity and high yield just by simple precipitation and washing, providing their direct use in primary biological assays without further purification.

Table 1. Liquid-phase synthesis of 3,5-disubstituted-1,2,4–triazoles on PEG support

Entry	R	Yield (%)[a]	Ee (%)[b]
1		92	96
2		99	95
3		98	93
4		99	94
5		73	93
6		99	90
7		90	87
8		89	88
9		92	85
10		88	90
11		95	95
12		99	99
13		78	89

[a] The yield based on the PEG-6000.
[b] Determined by chiral HPLC analysis.

Acknowledgements

The authors thank Natural Science Foundation of Gansu Province (ZS021-A25-006-Z) for the financial support of this work and Professor Guo-Ren Yue for analysis of NMR.

References and notes

1. (a) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489–509; (b) Wentworth, P.; Janda, K. D. *Chem. Commun.* **1999**, 1917–1924; (c) Toy, P. H.; Janda, K. D. *Acc. Chem. Res.* **2000**, *33*, 546–554.
2. (a) Zhao, X.; Metz, W. A.; Sieber, F.; Janda, K. D. *Tetrahedron Lett.* **1998**, *39*, 8433–8436; (b) Blettner, C. G.; Konig, W. A.; Quhter, G.; Stenzel, W.; Schotten, T. *Synlett* **1999**, 307–311; (c) Racker, R.; Doring, K.; Reiser, O. *J. Org. Chem.* **2000**, *65*, 6932–6939; (d) Luisa, G.; Giorgio, M.; Pietro, C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2504–2508.
3. (a) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716–3717; (b) Bednarski, M.; Maring, C.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 3451–3454; (c) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310–312; (d) Keck, G. E.; Li, X. Y.; Krishnamurthy, D. *J. Org. Chem.* **1995**, *60*, 5998–5999; (e) Li, L. S.; Wu, Y.; Hu, Y. J.; Xia, L. J.; Wu, Y. L. *Tetrahedron: Asymmetry* **1998**, *9*, 2271–2277; (f) Schaus, S. E.; Branalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403–405; (g) Gong, L. Z.; Pu, L. *Tetrahedron Lett.* **2000**, *41*, 2327–2331; (h) Lévêque, L.; Blanc, M. L.; Pastor, R. *Tetrahedron Lett.* **2000**, *41*, 5043–5046; (i) Long, J.; Hu, J.; Shen, X.; Ji, B.; Ding, K. *J. Am. Chem. Soc.* **2002**, *124*, 10–11; (j) Yamashita, Y.; Saito, S.; Ishitani, H.; Kobayashi, S. *Org. Lett.* **2002**, *4*, 1221–1223; (k) Du, H.; Ding, K. *Org. Lett.* **2003**, *5*, 1091–1093.
4. (a) Johannsen, M.; Yao, S.; Jørgensen, K. A. *Chem. Commun.* **1997**, 2169–2170; (b) Yao, S.; Johannsen, M.; Audrain, H.; Hazell, R. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 8599–8605.
5. (a) Evans, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 4895–4896; (b) Thorhauge, J.; Johannsen, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **1998**, *37*, 2404–2406; (c) Zhuang, W.; Thorhauge, J.; Jørgensen, K. A. *Chem. Commun.* **2000**, 459–460; (d) Gademann, K.; Chavez, D. E.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2002**, *41*, 3059–3061; (e) Juhl, K.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1498–1501.
6. (a) Johannsen, M.; Jørgensen, K. A.; Zheng, X. F.; Hu, Q. S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 299–301; (b) Oi, S.; Terada, E.; Ohuchi, K.; Kato, T.; Tachibana, Y.; Inoue, Y. *J. Org. Chem.* **1999**, *64*, 8660–8667.
7. Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 6968–6969.
8. (a) Li, Z.; Wang, J. K.; Wang, X. C. *Synth. Commun.* **2003**, *33*, 3563–3570; (b) Wang, X. C.; Wang, J. K.; Li, Z. *Chin. Chem. Lett.* **2004**, *15*, 635–638.
9. Miyashita, M.; Yamasaki, T.; Shiratani, T.; Hatakeyama, S.; Miyazawa, M.; Irie, H. *Chem. Commun.* **1997**, 1787–1888.
10. Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3558–3588.
11. The typical procedure:
    Preparation of PEG-bound **1**: At room temperature, dibutyl tin oxide (1 mmol) was added to the solution of acetoacetic ester (8 mmol) in anhydrous DMF (10 mL). After 0.5 h, the solution of PEG6000 (6 g, 2 mmol terminal hydroxyl groups) in warm and anhydrous DMF (20 mL) was added, and the resultant mixture was stirred at 100 °C for 6 h. After removal of the residue by filtration, Et_2O was added into the filtrate to precipitate the pale yellow solid (**1**), which was washed several times and dried under vacuum. The solid was stored for the next step of the synthesis. ^1H NMR (500 MHz, $CDCl_3$): δ 2.25 (s, 3H, CH_3), 3.48 (s, 2H, $COCH_2CO$), 3.53–3.79 (m, OCH_2CH_2O), 4.30 (t, 2H, OCH_2CH_2OCO).
    Preparation of PEG-bound **2** and **3**: According to the literature 9, **2** and **3** were synthesized successfully without any unexpectedness. The method of the isolation of PEG-bound **2** and **3** is similar to that of PEG-bound **1** and **4**.
    Preparation of PEG-bound **4**: A mixture of benzaldehyde (2 mmol) and PEG-bound diene **3** (0.25 mmol) in anhydrous THF (10 mL) was added into the mixture containing (*R*)-BINOL (0.25 mmol), Ti(O*i*-Pr)$_4$ (1 M in toluene, 0.15 mmol), crushed 4 Å MS (1 g), and THF (10 mL), which was heated at 40 °C for 3 h prior to use. The resultant mixture was stirred for 48 h under ice bath condition, and then THF was removed. A solution of $BF_3 \cdot Et_2O$ in CH_2Cl_2 (15 mL) was added to the above residue and was stirred for 1 h at room temperature. Then the solvent was removed and the residue was dissolved in 40 mL of 10% K_2CO_3, followed by extraction with CH_2Cl_2 (3×15 mL) and dried with $MeSO_4$. Et_2O was added to the corresponding solution to precipitate the PEG-bound dihydropyrones. After drying in vacuum, the solid was stored to be used in the next step of the synthesis.
    Preparation of 2-aryl-5-methoxylcarbonyl-dihydropyrones: A mixture of **4** (0.25 mmol) and 0.1 N MeONa in MeOH (10 mL) was stirred at room temperature for 5 h. Then Et_2O (40 mL) was added. The resulting precipitate was filtered and washed with Et_2O. The combined filtrates were washed with H_2O, dried with Na_2SO_4, and evaporated under reduced pressure to give the target product.
12. For compound **5a** is as follow: ^1H NMR (500 MHz, $CDCl_3$): δ 8.11 (s, 1H), 7.39–7.45 (m, 5H), 5.38–5.41 (m, 1H), 3.88 (s, 3H), 2.86–2.92 (m, 1H), 2.67–2.71 (m, 1H). ^{13}C NMR (200 MHz, $CDCl_3$): δ 190.52, 172.42, 166.47, 138.27, 128.80, 128.78, 126.05, 102.45, 80.76, 51.4, 42.31. MS: *m*/*z* 232(M^+), 234(M+2). Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21%. Found: C, 67.33; H, 5.19%.