Pergamon

Tetrahedron Letters 44 (2003) 7103–7106

TETRAHEDRON LETTERS

Liquid-phase synthesis of 2,3-dihydro-4-pyridones: one-pot three-component aza Diels–Alder reaction of Danishefsky's diene with aldehydes and PEG-supported amine

Hongchao Guo and Kuiling Ding*

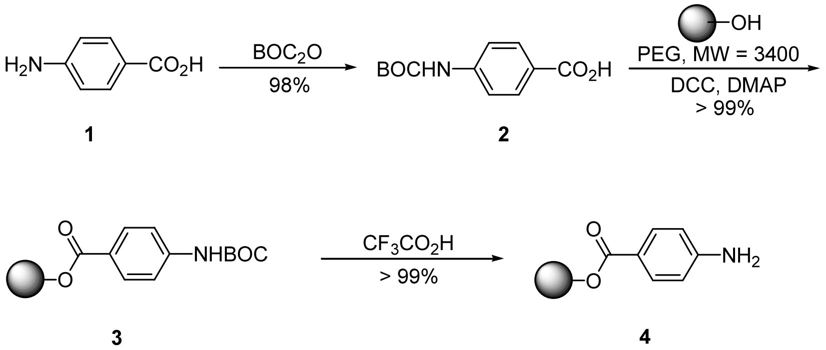
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, The Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, PR China

Received 12 May 2003; revised 23 June 2003; accepted 27 June 2003

Abstract—An efficient liquid-phase synthesis technique for the construction of 2,3-dihydro-4-pyridones on soluble polymer support has been developed, which utilized one-pot reaction of Danishefsky's diene with aldehydes and polymer-supported amine.

Solid-phase synthesis technique as a powerful tool has been applied successfully throughout the field of combinatorial chemistry.[1] However, the heterogeneous nature of this strategy might result in some problems, such as relatively low reactivity and selectivity, harsh reaction conditions and extended reaction time, as well as the difficulty for characterization of the insoluble polymer-supported compounds. Therefore, development of liquid-phase synthesis using soluble polymers could provide an excellent opportunity to overcome the shortages of solid-phase approach to combinatorial library production[2] and organic synthesis.[3] This has the advantages of liquid-phase reaction and easy separation/purification of the products in solid-phase synthesis. Moreover, the soluble polymer-bound species allow using routine analytical methods (NMR, TLC, or IR) to monitor the reaction process and to determine the structures of products attached to polymer support directly. Poly(ethylene glycol) (PEG) is one type of polymer which is soluble in many solvents, such as CH_2Cl_2, $CHCl_3$, THF, CH_3OH or H_2O at room temperature and can be precipitated from a solution by addition of diethyl ether, hexane, or *tert*-butyl methyl ether.[3b,4] Therefore, PEG can be considered as an ideal support for liquid-phase combinatorial synthesis in terms of its controllable solubility in different solvents.

The aza Diels–Alder reaction of Danishefsky's diene with imine has provided a convenient protocol for the synthesis of a type of nitrogen heterocycles, 2-substi-



Scheme 1. Synthesis of PEG-supported amine.

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* Corresponding author. Fax: 86-21-6416-6128; e-mail: kding@mail.sioc.ac.cn

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doi:10.1016/S0040-4039(03)01708-8

tuted 2,3-dihydro-4-pyridones, with important synthetic applications in natural or unnatural products.[5] Various Lewis acids such as $BF_3{\cdot}Et_2O$,[6] $ZnCl_2$,[7] or lanthanide triflates,[8] alkaline salt,[9] AgOTf,[10] and Brønsted acids, including HBF_4 and TsOH,[11] have been utilized to promote this reaction. This reaction could be also carried out under acid-free conditions by correct choice of reaction solvents.[12] Wilson reported a solid-phase synthesis of 2,3-dihydro-4-pyridones by the reaction of Danishefsky's diene with the Wang resin-supported imines.[13] However, to the best of our knowledge,[14] a liquid-phase synthesis using soluble polymer as the support has not yet been utilized in the aza Diels–Alder reaction. Herein, we reported a novel practical liquid-phase synthesis of 2,3-dihydro-4-pyridones *using PEG as a support through the aza Diels–Alder reaction in a three-component one-pot reaction manner.*

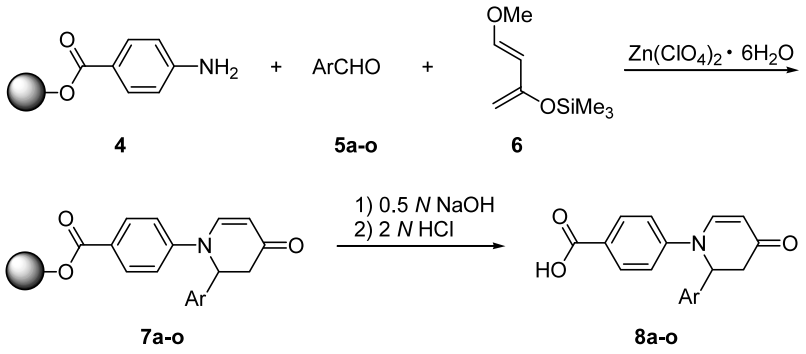
As shown in Scheme 1, 4-aminobenzoic acid (**1**) was first protected with BOC_2O following the literature procedure.[15] Then the BOC-protected aminobenzoic acid (**2**) was attached onto the soluble support by condensation with PEG (MW = 3400) in the presence of DCC (1,3-dicyclohexylcarbodiimide) and DMAP (4-dimethylaminopyridine). The reaction process was monitored by ^1H NMR analysis using $CDCl_3$ as the solvent. It was found that the condensation reaction completed after stirring for 24 h at room temperature. The PEG-supported Boc-protected amine **3** was obtained by precipitation in diethyl ether in >99% yield. The separated solid was redissolved in CH_2Cl_2/CF_3COOH (2/1) mixed solvent and the solution was stirred at room temperature for 24 h to remove BOC of **3**. The PEG supported amine **4** was separated quantitatively by precipitation again in diethyl ether. The preparation of **4** could be carried in a 0.1-mol scale without decrease of efficiency. Therefore, this procedure provided a practical synthesis of the PEG-supported aromatic amine.

With the PEG-supported amine **4** in hand, we switched our attention to its application in liquid-phase combinatorial synthesis. As shown in Scheme 2, the PEG-bound amine **4** reacted with 10 equiv. of aldehyde **5** and 12 equiv. of the Danishefsky's diene **6** in the presence of 0.1 equiv. of $Zn(ClO_4)_2{\cdot}6H_2O$ in methanol at room temperature for 12 h. After accomplishment of the reaction, the PEG-bound cycloadduct **7** was precipitated by addition of diethyl ether and was separated by simple filtration. Then, the separated solid of **7** was dissolved in 0.5N NaOH aqueous solution followed by stirring for 12 h at room temperature to cleave the product from the PEG support. The resulted solution after hydrolysis was acidified with 2N HCl solution and **8** was precipitated because of its poor solubility in water. Accordingly, 2-substituted *N*-(4-carboxyphenyl)-2,3-dihydro-4-pyridones (**8**) could be obtained by filtration and the structures were confirmed by ^1H NMR and MS spectra. In some cases, a trace amount of the PEG residue might contaminate the final products **8**. This problem could be easily solved by passing the crude product through a pad of silica gel using acetone-methanol (1:1) as the eluent. A variety of aromatic aldehydes could be used for this synthetic strategy. The desired compounds in most cases as shown in Table 1 were obtained in relatively high yields and purities.[16] It

Table 1. Liquid-phase synthesis of 2,3-dihydro-4-pyridones by aza Diels–Alder reaction

Entry	ArCHO (**5**)	Pyridones (**8**)	Yield (%)[a]	Purity (%)[b]
1	PhCHO (**a**)	**8a**	83	89
2	4-MeC_6H_4CHO (**b**)	**8b**	99	71
3	3-MeC_6H_4CHO (**c**)	**8c**	87	98
4	4-MeOC_6H_4CHO (**d**)	**8d**	96	79
5	3-MeOC_6H_4CHO (**e**)	**8e**	89	96
6	3-FC_6H_4CHO (**f**)	**8f**	92	70
7	4-ClC_6H_4CHO (**g**)	**8g**	44	84
8	3-ClC_6H_4CHO (**h**)	**8h**	99	77
9	4-BrC_6H_4CHO (**i**)	**8i**	95	82
10	3-BrC_6H_4CHO (**j**)	**8j**	31	72
11	4-NCC_6H_4CHO (**k**)	**8k**	80	48
12	$3,5\text{-F}_2C_6H_3CHO$ (**l**)	**8l**	84	60
13	$3,5\text{-Cl}_2C_6H_3CHO$ (**m**)	**8m**	58	39
14	2-Naphthaldehyde (**n**)	**8n**	84	82
15	Fufural (**o**)	**8o**	99	81
16[c]	4-ClC_6H_4CHO (**g**)	**8g**	90	66
17[c]	3-BrC_6H_4CHO (**j**)	**8j**	83	79
18[c]	$3,5\text{-Cl}_2C_6H_3CHO$ (**m**)	**8m**	78	82

[a] Isolated yield based on loading of original HO-PEG-OH.
[b] Purity determined by HPLC analysis of the crude products.
[c] The reaction time for cycloaddition step was reduced to 0.5 h.



Scheme 2. Synthesis of 2,3-dihydro-4-pyridines using soluble polymer-supported amine through aza Diels–Alder reaction.

is obvious that the aromatic aldehydes containing electron-donating group afforded the corresponding products in higher yields and purities than those substrates containing electron-withdrawing group. Particularly, in the cases of 4-Cl, 3-Br, 4-CN and 3,5-dichloro substituted benzaldehydes (entries 7, 10, 11 and 13), the purities of the products were relatively low. In principle, the electron-deficient imines should be favored for the aza hetero-Diels–Alder reaction with Danishefsky's diene. However, in our previous work we observed the same tendency of substituent effect on the yields of the reaction.[12] It was speculated that the cycloadducts containing electron-withdrawing groups might be unstable and decomposed during the reaction process. Accordingly, reducing the reaction time for cycloaddition step to 0.5 h afforded the corresponding products in improved yields or purities when the reactions of 4-Cl, 3-Br, 3,5-dichlorobenzaldehydes were taken as the substrates (entries 16–18). Therefore, reducing the reaction time is a key point for getting satisfactory results for the reaction of electron-withdrawing group substituted benzaldehydes. This should be considered when a parallel liquid-phase synthesis was performed using this strategy. Moreover, the reaction of 4-cycanobenzaldehyde under same experimental conditions gave the corresponding PEG-bound product **7k** in >90% conversion, but the purity of final product **8k** after hydrolysis was only ~50%. HPLC and HRMS analyses showed that the cyano group in the product **8k** was partially hydrolyzed into amide during the basic cleavage of polymer-supported product, and as a result, led to the low purity of product. The cycloaddition reactions of olefinic and aliphatic aldehydes (such as *trans*-cinnamaldehyde and 3-phenylpropionaldehyde) were also examined under various experimental conditions, but the conversion of PEG-bound amine for the formation of the corresponding PEG-bound products **7** was rather low (<50%).

In conclusion, we have developed a novel liquid-phase synthesis of 2,3-dihydro-4-pyridones by a one-pot three-component reaction of the soluble polymer (PEG) supported amine, aromatic aldehydes, and the Danishefsky's diene. The polymer-bound 2,3-dihydro-4-pyridone provides a useful scaffold for other synthetic transformations.[17] The research on the aza Diels–Alder reaction using the PEG-supported aldehydes, the application of this strategy to the library production and its asymmetric version using the soluble polymer supported substrates is being carried out in this laboratory and will be reported in due course.

Acknowledgements

Financial support from the National Natural Science Foundation of China, the Chinese Academy of Sciences, the Major Basic Research Development Program of China (Grant No. G2000077506) and the Science and Technology Commission of Shanghai Municipality are gratefully acknowledged.

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16. A typical procedure for the synthesis of 1-(4-carboxyphenyl)-2-(4-methoxyphenyl)-2,3-dihydro-4-pyridone (Table 1, entry 4) is as follows: the PEG supported amine **4** (0.23 g, 6.25×10^{-2} mmol, containing all 0.13 mmol NH_2), 4-methoxybenzaldehyde (0.15 mL, 1.25 mmol), $Zn(ClO_4)_2 \cdot 6H_2O$ (4.65 mg, 1.25×10^{-2} mmol) and the Danishefsky's diene (0.40 mL, 75% purity, 1.50 mmol) were added to 0.5 mL of methanol and the reaction

mixture was stirred for 12 h at room temperature. After completion of the reaction, 40 mL of diethyl ether to allow the precipitation of the PEG-bound product **7**, which was collected by filtration and washed with diethyl ether for three times. The obtained product **7d** was dissolved in 2 mL of 0.5N NaOH aqueous solution and stirred at room temperature overnight. Then, the solution was acidified to pH 2–3 using 2N HCl and the final product **8d** was precipitated. After filtration, the collected solids were redissolved in small amount of methanol/acetone (1/1) mixed solvent and the solution was allowed to pass through a short silica gel column with methanol/acetone (1/1) as the eluent. The combined filtrate was evaporated under reduced pressure to give the product **8d** as a pale yellow solid (38.7 mg, 96% yield). The purity of this compound was determined to be 79% by HPLC analysis. ^{1}H NMR (300 MHz, methanol-d_4) δ 8.06 (d, 1H), 7.94 (d, 2H), 7.18 (t, 4H), 6.86 (d, 2H), 5.48 (d, 1H), 5.27 (d, 1H), 3.74 (s, 3H), 3.32 (q, 1H), 2.70 (dd, 1H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 190.0, 167.2, 158.5, 147.1, 146.8, 130.7, 129.4, 127.3, 116.6, 114.2, 103.3, 69.8, 59.0, 55.0, 43.3; HRMS found: 323.1161(calcd for $C_{19}H_{17}NO_4$, 323.1159).

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