Development of 3-methoxy-4-benzyloxybenzyl alcohol (MBBA) resin as polymer-supported synthesis support: Preparation and benzyl ether cleavage by DDQ oxidation

QIANG HUANG [1],*, BAO-ZHONG ZHENG[1] and QUAN LONG[2]

[1]Department of Materials Science and Engineering, Yunnan University, Kunming, Yunnan 650091, PR China
[2]School of Chemical Science and Engineering, Yunnan University, Kunming, Yunnan 650091, PR China
e-mail: huangqiang@ynu.edu.cn

Abstract. 3-Methoxy-4-benzyloxybenzyl alcohol (MBBA) resin was synthesized by a two-step sequence under microwave irradiation involving the reaction of commercially available Merrifield resin with vanillin, followed by reduction with sodium borohydride. MBBA resin was treated with bromides in the presence of sodium hydride to afford the corresponding resin-bound benzyl ethers. Cleavage of the resin-bound benzyl ethers from the MBBA resin was carried out using 2,3-dichloro-5,6-dicyano-benzoqunone (DDQ) to give the corresponding alcohols in good yields. Moreover, the recovery, regeneration, and reuse of this polymer support could be achieved easily. MBBA resin can be developed as a kind of solid-phase synthesis bead of alcohols.

Keywords. Solid-phase organic synthesis; polymer support; linker; 3-methoxy-4-benzyloxybenzyl alcohol resin; DDQ oxidation; recycling.

1. Introduction

Solid-phase organic synthesis (SPOS) continues to be important in the development of libraries of new molecules since it offers advantages such as the ease of reaction work-up and automation.[1] The success of a SPOS strategy depends on the properties of the solid supports in many critical ways.[2] The solid supports used most widely in SPOS are Merrifield resin and their derivatives with various linkers which are the structural bridges between the polymer framework and a substrate. Most linkers for solid-phase chemistry are derived from known protecting groups, and hereby they have been described as the immobilized protecting groups since many of them bear some similarities to protecting groups in solution phase synthesis.[3] For example, they are required to be stable to the reaction conditions when used during the elaboration of the target molecule, and be cleaved selectively and orthogonally at the end of

the synthesis, so that the target molecule can be released from the resin into solution.[3b,3d]

On the other hand, 4-methoxybenzyl (MPM) and 3,4-dimethoxybenzyl (DMPM) protecting groups are widely applied in solution phase synthesis for their benzyl formations readily removed by 2,3-dichloro-5,6-dicyano-benzoqunone (DDQ) oxidation under mild and neutral conditions.[4] Thus, one of the present authors (Zheng *et al*) used them skillfully for the synthesis of the complex natural products.[5] Resin-bound MPM protecting groups, whose *p*-alkoxylbenzyl system could be selectively cleaved by DDQ oxidation for the release of target molecules, have been applied for SPOS of alcohols and amines.[6] However, DMPM group, a more sensitive group than MPM group for DDQ removing,[4b] has not been developed for any SPOS strategies in our knowledge. In this work, we prepared a novel 3-methoxy-4-benzoxybenzyl alcohol (MBBA) resin, and it was reacted with various bromides to form the benzyl ether systems which contain the resin-bound DMPM group. The benzyl ether systems cleaved by DDQ oxidation were studied for the potential application of SPOS for alcohols.

*For correspondence

2. Experimental

2.1 *Genneral*

Merrifield resin (200–400 mesh, 1% DVB cross-linked, 1·24 mmolCl/g) was obtained from Tianjin Nankai Hecheng Technological Com. Ltd., China, and was extracted by EtOH before it was used. Vanillin, DDQ, 4-nitrobenzyl bromide, 4-cyanobenzyl bromide, 3-bromoethyl cyanide, and *N,N*-diethyl-2-bromo-acetamide were purchased from Merck, Germany. Other chemicals were obtained locally. THF and DCM were distilled before using. Microwave reactions were conducted using a CEM Discover Synthesis Unit. Reactions were performed in glass vessels. DDQ oxidation cleavages were performed using KEM-6 Parallel Synthesizer. Elemental analysis was carried out by GmbH Vario EL. Agilent 1100 was used for HPLC. FT-IR spectra (KBr tableting) were recorded on Thermo Nicolet TFIR AVATAR 360. ^{1}H-NMR spectra were recorded using Bruker AVANCE DRX500 spectrometer with special high resolution magic angle spinning (HR-MAS) probe and the resin was placed in a 4 mm rotor. Chemical shifts were recorded in parts per million (δ: ppm) referenced to TMS (δ: 0) as an internal standard. Coupling constants (J) are given in Hertz (Hz).

2.2 *Syntheses and characterization*

2.2a *3-methoxy-4-benzoxylbenzyl aldehyde resin* (**1**): Merrifield resin (1 g, 1·24 mmol g^{-1}, 1·24 mmol) was placed in a reaction vessel and allowed to swell in DMF (5 mL) for 30 min under N$_2$. Vanillin (300 mg, 1·972 mmol), K$_2$CO$_3$ (400 mg, 2·894 mmol), and tetrabutyl ammonium iodide (TBAI, 54 mg, 0·146 mmol) were dissolved in DMF (15 mL) and added via syringe to the reaction vessel. The mixture was stirred and heated in the microwave at 120°C for 5 min. After cooling to room temperature, the beads were transferred to a sintered tube and washed successively with acetone–CH$_3$OH–H$_2$O (1 : 1 : 1) (10 mL × 5), acetone (10 mL × 3), THF (10 mL × 3), CH$_3$OH (10 mL × 3), then dried under vacuum at 50°C for one hour to give somewhat yellow beads. IR (KBr): 1688 cm^{-1} (C=O), 2760 cm^{-1} (O=C–H). ^{1}H-NMR (500 MHz, CDCl$_3$): δ 9·78 (1H, *s*, CHO), 7·30 (2H, *br s*, H-Ar), 6·98 (*br s*, PS), 5·11 (2H, *br s*, CH$_2$O), 3·70 (3H, *br s*, CH$_3$O), 1·73 (*br s*, PS), 1·38 (*br s*, PS). The loading of resin

(**1**) was determined by N elemental analysis involving DNP derivative reaction. Resin (**1**) (20 mg) was placed in a tube and swelled in DMF (3 mL) for 15 min. DNP (3 equiv.) and a catalytic amount of acetic acid were added to the tube, then it was sealed and placed in an oscillator for 30 min at room temperature. The mixture was filtered, washed and dried under vacuum. Theoretical loading = 1·087 mmol g^{-1}. Found: C, 78·59; H, 6·35; N, 6·06.

2.2b *MBBA resin* (**2**): Resin (**1**) (992 mg, 1·081 mmol g^{-1}, 1·074 mmol) was placed in a reaction vessel and allowed to swell in THF (5 mL) for 30min under N$_2$. NaBH$_4$ (150 mg, 3·97 mmol) and TBAI (75 mg, 0·203 mmol) were dissolved in mixed solvent containing THF (10 mL) and H$_2$O (2 mL) and the mixture was injected. The contents were stirred and heated in the microwave at reflux for 10 min. The resultant solid was filtered, washed with ethyl acetate (20 mL), water (3 × 10 mL), acetone (2 × 10 mL), CH$_2$Cl$_2$ (2 × 20 mL) and ether (2 × 10 mL). The resin was dried at 50°C for one hour to give white beads. IR (KBr): 3108, 3312 cm^{-1}. ^{1}H-NMR (500 MHz, CDCl$_3$): δ 7·13 (*br s*, PS), 7·01 (*br s*, PS), 6·60 (3H *br s*, H-Ar), 4·92 (2H *br s*, CH$_2$O), 3·82 (3H, *br s*, CH$_3$O), 2·05 (1H, *s* OH), 1·69 (*br s*, PS), 1·33 (*br s*, PS). The loading of resin (**2**) was determined by N elemental analysis involving 4-nitrobenzoyl chloride derivative reaction. Resin (**2**) (20 mg) was placed in a tube and swelled in DMF (2 mL) for 15 min. 4-Nitrobenzoyl chloride (3 equiv.), a catalytic amount of 4-dimethylamino pyridine (DMAP) and pyridine were added to the tube, then it was sealed and placed in an oscillator for 30 min at room temperature. The mixture was filtered, washed and dried under vacuum. Theoretical loading = 1·086 mmol g^{-1}. Found: C, 80·13; H, 8·35; N, 1·49.

2.3 *General procedure for the preparetion of the resins* (**3a–d**)

To resin (**2**) (200 mg, 1·064 mmol g^{-1}, 0·210 mmol) was added NaH (15·4 mg, 0·642 mmol) under N$_2$ atmosphere. One of the bromides (4·0 equiv.) in dry DMF (5 mL) was injected. The contents were shaken for 6 h at 60°C. The resultant solid was filtered, washed with H$_2$O (2 × 5 mL), 3% acetic acid (2 × 5 mL), H$_2$O (2 × 5 mL), acetone (2 × 5 mL), CH$_2$Cl$_2$ (2 × 5 mL) and ether (2 × 5 mL). The resins were dried in vacuum to corresponding resin-bound
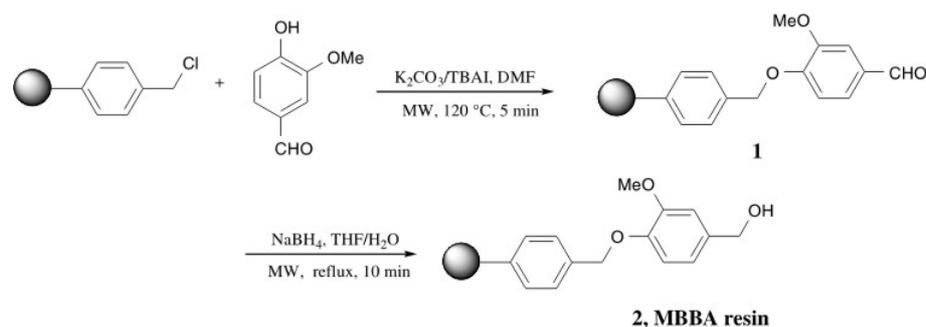
Scheme 1.   The synthetic process of MBBA resin.

benzyl ethers. Theoretical loading: (**3a**), 0·930 mmol g^{-1}; (**3b**), 0·948 mmol g^{-1}; (**3c**), 1·007 mmol g^{-1}; (**3d**), 0·950 mmol g^{-1}. Found: (3a), C, 76·52, H, 8·13, N, 1·28; (**3b**), C, 81·90, H, 8·46, N, 1·30; (**3c**), C, 78·93, H, 9·55, N, 1·36; (**3d**), 79·11, 10·10, N, 1·24.

2.4 General procedure for the DDQ cleavage of resin-bound benzyl ethers

To resin-bound benzyl ethers (**3a–d**, 200 mg) was respectively added DDQ (1·2 equiv.) in CH$_2$Cl$_2$–H$_2$O (10 : 1, 5 mL). The contents were shaken for 30 min at room temperature. The solid was filtered, washing with CH$_2$Cl$_2$–H$_2$O (10 : 1, 2 × 5 mL). The combined filtrate was analysed by HPLC.

3. Results and discussion

3.1 Synthesis of MBBA resin

MBBA resin was prepared by a two-step sequence under microwave irradiation involving the reaction of commercially available Merrifield resin with vanillin, followed by reduction with sodium borohydride as shown in scheme 1. In the first step, Merrifield resin was reacted with vanillin in the presence of non-nucleophilic base K$_2$CO$_3$, a catalytic amount of TBAI as phase transfer catalyst, and DMF as solvent under microwave irradiation at 120°C only for 5 min as described in our previous work.[7] 3-Methoxy-4-benzoxyl benzaldehyde resin (**1**) was simply obtained by filtration of the reaction mixture and washing the resultant solid by various solvents. The formation of resin (**1**) was monitored by the appearance of C=O (1688 cm^{-1}) and O=C–H (2760 cm^{-1}) stretching frequency of polymer-supported benzaldehyde group in FTIR analysis, further verified by the characteristic aldehydic reso-

nance at 9·78 ppm in the ^{1}H MAS-NMR spectrum. Loading of the aldehyde group was determined by nitrogen analysis involving 2,4-dinitrophenyl hydrazine (DNP) derivative, to be 1·081 mmol/g, corresponding to 99% yield. Next, reduction of the resin (**1**) with NaBH$_4$ under microwave-assisted phase transfer catalytic condition in mixed solvent THF/H$_2$O at reflux temperature for 10 min afforded the MBBA resin (**2**) according to our work reported recently.[8] The monitoring of reaction was performed by the FTIR spectrum resorting the disappearance of benzaldehyde group stretching frequency and the appearance of OH vibrational frequency and by the ^{1}H MAS-NMR spectrum with the help of the disappearance of aldehydic resonance at 9·78 ppm. The OH loading of resin (**2**) was determined to be 1·064 mmol/g by nitrogen analysis involving 4-nitrobenzoyl chloride derivative, corresponding to 98% yield.

The syntheses of 4-benzoxylbenzyl alcohol resins have been reported earlier.[9] The methoxide-catalysed displacement of benzyl chlorine of Merrifield resin by 4-hydroxybenzyl alcohol (Wang resin)[9a] or 2-methoxy-4-hydroxybenzyl alcohol (Sasrin resin)[9b] was performed. Accordingly, MBBA resin would be synthesized by the reaction of chloromethyl resin with 3-methoxy-4-hydroxybenzyl alcohol (vanillic alcohol) under the similar condition. However, we found that the target resin could hardly be attained when we prepared the MBBA resin by the reaction of commercially available Merrifield resin with vanillic alcohol under methoxide-catalysed condition. It was likely to be the instability and polymerization of *p*-hydroxy-benzyl alcohols in base.[10] Furthermore, the electronic effects of the 3-methoxy group of vanillic alcohol may deleteriously facilitate the polymerization in alkali medium compared with the species without methoxy group. Since the direct loading of vanillic alcohol to polymer support was unsuccessful, a relatively indirect

method involving functional group transformation would be taken into account. Resin (**1**) could be readily prepared by the phase transfer catalysed reaction of Merrifield resin with vanillin in good yield.[11] Vanillin being different from vanillic alcohol, the electronic effects of vanillin's *o*-methoxy group may significantly enhance the nucleophilicity of the phenolic OH because of the existence of formyl group, and can promote the formation of corresponding benzaldehyde resins.[11a] Then, reduction of solid-supported aldehyde to corresponding benzyl alcohol could obtain the MBBA resin (**1**). Though a tow-step sequence was involved in current process, the microwave irradiation assisted method could

Table 1. Etherization of (**2**) with bromated species

3a-d

Entry	RBr	Reaction time/h	Yield (%)
1	Br—CH₂—C₆H₄—NO₂	6	98
2		6	98
3	Br—CH₂—C₆H₄—CN		98[a]
4			97[b]
5			95[c]
6	Br—CH₂CH₂—CN	6	97
7	Br—CH₂—C(O)—NEt₂	12	93

[a]With the first regenerated resin (**2**). [b]With the second regenerated resin (**2**). [c]With the third regenerated resin (**2**)

Table 2. Cleavage of the resin-bound benzyl ethers.

3a-d → **4a-d**

Entry	ROH	Reaction time/min.	Yield[a] (%)
1	HO—CH₂—C₆H₄—NO₂	30	98
2	HO—CH₂—C₆H₄—CN	30	99
3	HO—CH₂CH₂—CN	60	91
4	HO—CH₂—C(O)—NEt₂	45	94

[a]Yield according to HPLC data, product was not isolated

accelerate the processing and greatly decreased the reaction time.
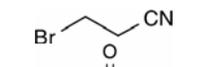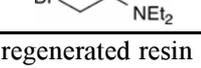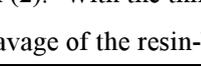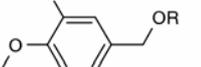
3.2 *Cleavage of resin-bound benzyl ethers*

Various bromides containing nitrogen, including 4-nitrobenzyl bromide, *p*-cyanobenzyl bromide, 3-bromoethyl cyanide, or *N,N*-diethyl-2-bromo-acetamide, was respectively reacted with resin (**2**) in the presence of NaH so as to provide the corresponding polymer-supported benzyl ethers (**3a–d**). The separation and purification of polymer-supported benzyl ethers were simply treated by filtration and washing. The loading rates of various solid-supported benzyl ethers were determined by elemental analysis. The results presented in table 1. As can be seen, the loading rates of various benzyl ethers exceed 90%, and the good loadings were obtained.

Then, the resin-bound 3-methoxy-4-benzoxyl-benzyl ether systems were cleaved with DDQ (1·2 equiv.) oxidation in dichloromethane containing a small amount of water at room temperature for a quite short time to lead to formation of the corresponding alcohols (**4a–d**) in high yield (table 2). Comparison with the previous report of Deegan and his coworkers,[6a] the benzyl ether system of MBBA resin cleaved by DDQ exhibited similar yields though the AgroGel-Wang derived ether resins have a PEG chain spacer which makes its activity higher.[12]

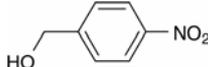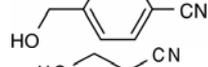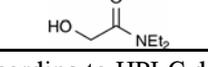## 3.3 *Regeneration and recycling*

One of the major advantages for development of the current strategy is the potential recovery of the polymer beads for subsequent reuse. The 3-methoxy-4-benzoxyl benzaldehyde resin (**1**) could be recovered quantitatively by simple filtration and washing with organic solvents after DDQ cleavage was performed. Transmittance FTIR and ^{1}H-NMR spectra of the recovered polymer beads showed the restoration of the aldehyde functional group, with a loading similar to the original value. Next, the MBBA resin (**2**) could be regenerated by reduction with NaBH₄. The process of the regeneration and recycling for the polymer beads was schematically presented in figure 1. The OH loading of the first, second, and third-hand resin 2 was hardly decreased to compare that of the freshly resin, and the recovered resin could be reused for the same reactions
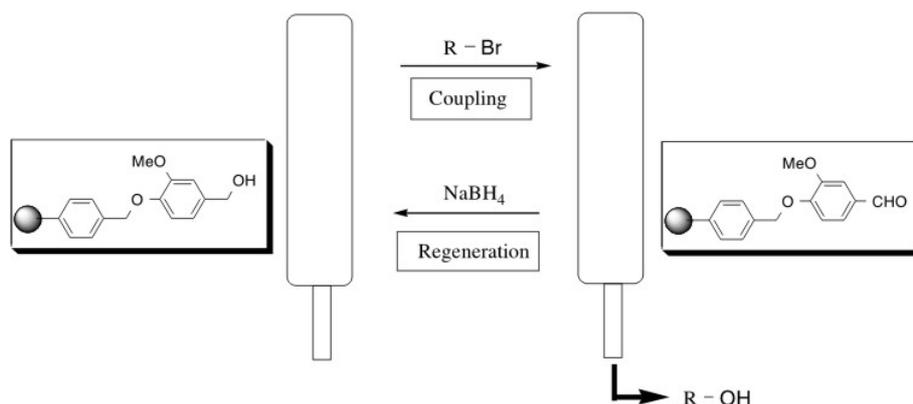
Figure 1. Repeated use of the polymer beads.

without loss of chemical yield of the resin-bound etherification products (table 1, Entry 3–5).

4. Conclusion

In summary, a simple and efficient two-step sequence synthesis of a novel 3-methoxy-4-benzoxylbenzyl alcohol (MBBA) resin involving linking vanillin to Merrifield resin, followed by reduction with NaBH$_4$, and effective DDQ cleavage of solid-supported benzyl ethers were successfully carried out to obtain alcohol products. Moreover, recovery, regeneration, and reuse of the resin were achieved. In short, MBBA resin can be developed as a kind of solid-phase synthesis beads of alcohols and others, and the polymer beads can be duty-cycle operation.

References

1. (a) Boldt G E, Dickerson T J and Janda K D 2006 *Drug Discovery Today* **11** 143; (b) Diaz-Garcia M E, Pina-Luis G and Rivero I A 2006 *Trends Anal. Chem.* **25** 112; (c) Shimomura O, Lee B S, Meth S, Suzuki H, Mahajan S, Nomura R and Janda K D 2005 *Tetrahedron* **61** 12160
2. (a) Walsh D, Wu D and Chang Y-T 2003 *Curr. Opin. Chem. Biol.* **7** 353; (b) Vaino A R and Janda K D 2000 *J. Comb. Chem.* **2** 279; (c) Czarnik A W 1998 *Biotechnol. Bioeng.* **61** 77
3. (a) Guillier F, Orain D and Bradley M 2000 *Chem. Rev.* **100** 2091; (b) Orain D, Ellard J and Bradley M 2002 *J. Comb. Chem.* **4** 1; (c) Huang Q, Long Q and Zheng B-Z 2004 *Prog. Chem.* **16** 236; (d) James I W 1999 *Tetrahedron* **55** 4855; (d) Brown A R, Hermkens P H H, Ottenheijm H C J and Rees D C 1998 *Synlett* 817
4. (a) Oikawa Y, Yoshioka T and Yonemistu O 1982 *Tetrahedron Lett.* **23** 885; (b) Horyta K, Yoshioka T, Tanaka T, Oikawa Y and Yonemistu O 1986 *Tetrahedron.* **42** 3021
5. (a) Zheng B-Z, Yamauchi M, Dei H, Kusaka S, Matsui K and Yonemitsu O 2000 *Tetrahedron Lett.* **41** 6441; (b) Matsui K, Zheng B-Z, Kusaka S, Kuroda M, Yoshimoto K, Yamada H and Yonemitsu O 2001 *Eur. J. Org. Chem.* 3615; (c) Zheng B-Z, Maeda H, Mori M, Kusaka S, Matsushima T, Nakajima N, Uenishi J and Yonemitsu O 1999 *Chem. Pharm. Bull.* **47** 1288; (d) Zheng B-Z, Yamauchi M, Dei H and Yonemitsu O 2000 *Chem. Pharm. Bull.* **48** 1761
6. (a) Deegan T L, Gooding O W, Baudart S and Porco J A 1997 *Tetrahedron Lett.* **38** 4973; (b) Kobayashi S and Aoki Y 1998 *Tetrahedron Lett.* **39** 7345; (c) Kobayashi S and Akiyama R 1998 *Tetrahedron Lett.* **39** 9211
7. Huang Q, Li Z, Ma X, Long Q and Zheng B-Z 2007 *Acta Polym. Sin.* **7** 681
8. Huang Q, Long Q and Zheng B-Z 2008 *Acta Polym. Sin.* **5** 487
9. (a) Lu G S, Mojsov S, Tam J P and Merrifield R B 1981 *J. Org. Chem.* **46** 3433; (b) Mergler M, Tanner R, Gosteli J and Grogg P 1988 *Tetrahedron Lett.* **32** 4005
10. Katritzky A R, Toader D, Watson K and Kiely J S 1997 *Tetrahedron Lett.* **38** 7849
11. (a) Sarhan A A, El-Shehawy A A and Abdelaal M Y 2002 *React. Funct. Polym.* **50** 139; (b) Huang Q, Long Q, Shi M X and Zheng B-Z 2005 *Chin. J. Funct. Polym.* **18** 32
12. (a) Porco J A, Deedan T, Devonport W, Gooding O W, Heisler K, Labadie J W, Newcomb B, Nguyen C, van Eikeren P, Wong J and Wright P 1997 *Mol. Divers.* **2** 197; (b) Cardona C M, Jannach S H, Huang H, Itojima Y, Leblam R M and GamLey R E 2002 *Helv. Chim. Acta* **85** 3532