Novel Synthesis of *N*-Substituted *p*-Hydroxybenzoic Amides on Soluble Polymer-Support

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The synthesis of *N*-substituted *p*-hydroxybenzoic amides using a liquid phase approach is described. Poly(ethylene glycol) (PEG) and *p*-hydroxybenzoic acid were linked by oxalyl chloride to give compound 1, which was chlorinated by thionyl chloride, followed by amidation with NHR^1R^2 to yield compound 3. Hydrolysis of compound 3 gave the title amide 4. These crude library members were obtained in good yields with high purities.

Keywords amide, poly(ethylene glycol), synthesis

Introduction

The growing application of combinatorial organic synthesis[1] on solid support has been reflected in the rapidly increasing reaction types and synthetic strategis. It has been regarded as an important tool for the synthesis of a large number of interesting compounds for pharmaceutics *etc*. Coupled with high-capacity screening systems, this technology may lead to revolution of the way to develope new drug discovery process. However, the solid-phase approach often requires additional research and development time. Now many research efforts are focused on liquid-phase combinatorial synthesis (LPCS) using soluble polymer support such aspoly(ethylene glycol) (PEG) to generate libraries.[2-4] This macromolecular carrier is soluble in most organic solvents such as CH_2Cl_2, CH_3CN *etc*. and has a strong tendency to precipitation in certain solvents such as $(CH_3CH_2)_2O$, $(CH_3)_2CHOH$ *etc*. After complete reaction, the product bound to the support can be purified by simple way involved in filtering and washing away the unwanted material.

Various amides have been found to possess widespread pharmacological and biological activity[5,6] and been synthesized with conventional solution-phase[7] or solid-phase reactions.[8] However, there is difficulty in purification of products in solution-phase reaction or monitoring the reaction progress and characterization of intermediates in solid-phase reaction.[9] Therefore, practical methods of rapidly synthesizing various amides are of great interest in drug discovery. As part of our continuing effort to utilize soluble polymer-supported systems in organic synthesis,[10-12] liquid phase synthesis of *N*-substituted *p*-hydroxybenzoic amides on soluble polymer support with oxalyl chloride as the linker has been reported.[10] The procedure described in Scheme 1 is utilized for the synthesis of a representative library

Experimental

All organic solvents and bases were dried by standard method. PEG was dried by azeotropic distillation with toluene. Melting points were determined on an electrothermal melting point apparatus and uncorrected. IR spectra were recorded on an IR-Spectrum one (PE) spectrometer. ^1H NMR spectra were record on a JNM-FX 90Q (JEOL) (90 MHz) in $CDCl_3$ or DMSO using TMS as internal standard. Elemental analysis was obtained on a PE 2400 CHN analyzer.

General procedure for the preparation of compounds **4**

To an ice-cold solution of oxalyl chloride (1.94 mmol, 0.17 mL) in 10 mL of CH_2Cl_2 in a 500-mL round bottom flask fitted with a magnetic stirrer, cooling bath and dropping funnel, a solution of PEG 3400 (3 g, 0.88 mmol), pyridine (0.31 mL) and 20 mL of CH_2Cl_2 was added. After 2 h, *p*-hydroxybenzoicacid was added and the mixture was stirred for 18 h at r.t. to give compound **1**. After precipitation of **1** by cold ether, two drops of dimethyl formamide (DMF) were added to a solution of **1** in thionyl chloride (25 mL). The mixture was refluxed for 4 h. Excess thionyl chloride was removed under vacuum to yield a brown solid **2**. Then NHR^1R^2 (1.94 mmol) and 25 mL of CH_2Cl_2 were added to the flask containing **2** and agitated at r.t. for 6 h. Compound **3** was obtained by precipitation, washed with cold ether and filtrated, and then hydrolyzed with 6% $NH_3 \cdot H_2O$ and acidified with 2 mol/L HCl to yield solid **4**. During the course of each sequence, TLC was used to detect the reaction progress and purity of PEG-bound intermediates. Finally, the slurry was filtered, the obtained solid was washed with 3 × 5 mL of water and

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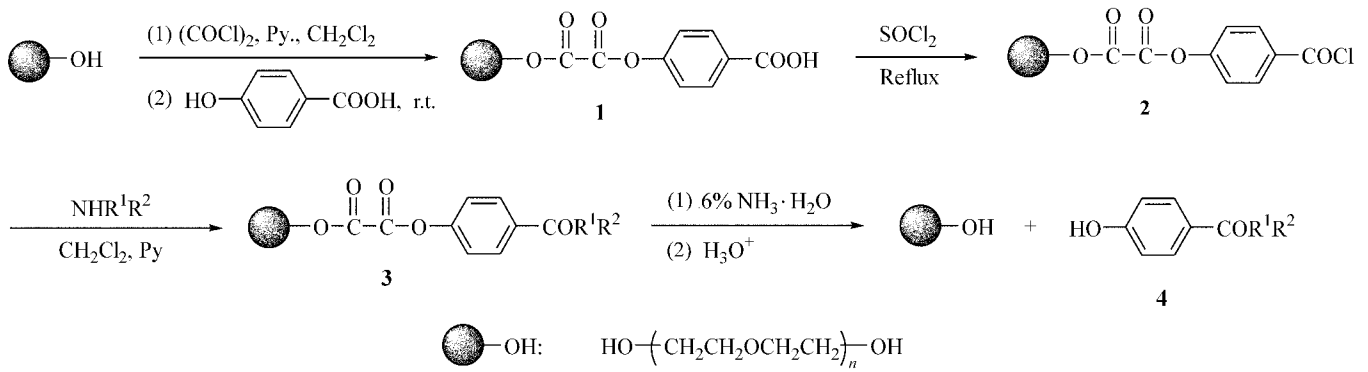
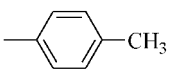
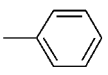
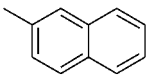
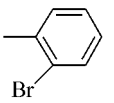
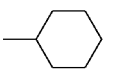
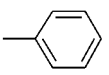
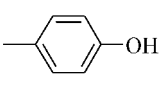
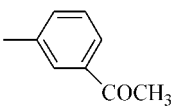
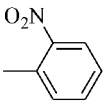
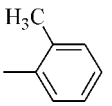
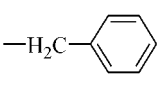
Scheme 1



NHR^1R^2	**a**	**b**	**c**	**d**	**e**	**f**
R^1				$-CH(CH_3)_2$		
R^2	H		H	$-CH(CH_3)_2$	H	H

NHR^1R^2	**g**	**h**	**i**	**j**	**k**	**l**
R^1						$-CH_2(CH_2)CH_3$
R^2	H	H	H	H	H	H

recrystallized from EtOH-H_2O, the product was given by drying under vacuum at 60 ℃ for 6 h. All compounds **4a—4l** were prepared according to the similar way. The physical and spectral data of compounds **4a—4l** are reported below. Yields are based on weight of crude sample after cleavage from the support.

4a Yield 47.8%, m.p. 254—255 ℃; ^{1}H NMR (DMSO-d_6) δ: 10.11 (s, 1H, NH), 9.82 (s, 1H, OH), 6.80—7.91 (m, 8H, ArH), 3.74 (s, 3H, OCH_3); IR (KBr) ν: 3408 (OH), 3319 (NH), 1639 (CO) cm^{-1}. Anal. calcd for $C_{14}H_{13}O_3N$: C 69.14, H 5.35, N 5.76; found C 69.12, H 5.30, N 5.79.

4b Yield 51.8, m.p. 211—212 ℃; ^{1}H NMR (DMSO-d_6) δ: 9.84 (s, 1H, OH), 6.65—7.33 (m, 14H, ArH); IR (KBr) ν: 3340 (OH), 3306 (NH), 1630 (CO) cm^{-1}. Anal. calcd for $C_{19}H_{15}O_2N$: C 78.62, H 5.52, N 4.83; found C 78.58, H 5.59, N 4.78.

4c Yield 49.2%, m.p. 255—256 ℃; ^{1}H NMR (DMSO-d_6) δ: 10.22 (s, 1H, NH), 8.35 (s, 1H, OH), 6.82—7.91 (m, 11H, ArH); IR (KBr) ν: 3345 (OH), 3307 (NH), 1643 (CO) cm^{-1}. Anal. calcd for $C_{17}H_{13}O_2N$: C 77.57, H 4.94, N 5.32; found C 77.51, H 4.90, N 5.38.

4d Yield 50.5%, m.p. 238—239 ℃; ^{1}H NMR (DMSO-d_6) δ: 9.62 (s, 1H, OH), 6.85—7.36 (m, 4H, ArH), 3.42—3.80 (m, 2H, CH), 1.12, 1.30 (d, J = 5.6 Hz, 12H, CH_3); IR (KBr) ν: 3235 (OH), 1603 (CO) cm^{-1}. Anal. calcd for $C_{13}H_{19}O_2N$: C 70.88, H 8.60, N 6.33; found C 70.81, H 8.54, N 6.35.

4e Yield 48.5%, m.p. 167—168 ℃; ^{1}H NMR (DMSO-d_6) δ: 9.13 (s, 1H, NH), 8.74 (s, 1H, OH), 6.82—8.10 (m, 8H, ArH); IR (KBr) ν: 3240 (OH), 3223 (NH), 1652 (CO) cm^{-1}. Anal. calcd for $C_{13}H_{10}O_2NBr$: C 67.53, H 4.33, N 6.06; found C 67.51, H 4.38, N 6.04.

4f Yield 51.6%, m.p. 256—257 ℃; ^{1}H NMR (DMSO-d_6) δ: 10.24 (s, 1H, NH), 9.70 (s, 1H, OH), 6.62—7.80 (m, 4H, ArH), 3.76—3.90 (m, 1H, NCH), 1.22—1.80 (m, 10H, $5CH_2$); IR (KBr) ν: 3318 (OH), 3200 (NH), 1620 (CO) cm^{-1}. Anal. calcd for $C_{13}H_{17}O_2N$: C 71.23, H 7.76, N 6.39; found C 71.31, H 7.79, N 6.35.

4g Yield 52.6%, m.p. 123—124 ℃; ^{1}H NMR (DMSO-d_6) δ: 10.64 (s, 1H, NH), 9.36 (s, 1H, OH), 9.05 (s, 1H, OH), 6.82—7.90 (m, 8H, ArH); IR (KBr) ν: 3390 (OH), 3278 (NH), 1698 (CO) cm^{-1}. Anal. calcd for $C_{13}H_{11}O_3N$: C 68.12, H 4.80, N 6.11; found C 68.10, H 4.83, N 6.13.

4h Yield 47.5%, m.p. 237—238 ℃; ^{1}H NMR (DMSO-d_6) δ: 10.12 (s, 1H, NH), 9.90 (s, 1H, OH), 6.82—8.36 (m, 8H, ArH), 2.62 (s, 3H, CH_3); IR (KBr) ν: 3399 (OH), 3170 (NH), 1650 (CO) cm^{-1}. Anal. calcd for $C_{15}H_{13}O_3N$: C 70.59, H 5.10, N 5.49; found C 70.57, H 5.09, N 5.52.

4i Yield 48.6%, m.p. 188—189 ℃; ^{1}H NMR (DMSO-d_6) δ: 9.90 (s, 1H, NH), 9.72 (s, 1H, OH), 6.81—8.16 (m, 8H, ArH); IR (KBr) ν: 3402 (OH), 3294 (NH), 1654 (CO) cm^{-1}. Anal. calcd for $C_{13}H_{10}O_4N_2$: C 60.47, H 3.88, N 10.85; found C 60.48, H 3.90, N 10.91.

4j Yield 49.6%, m.p. 209—210 ℃; ^{1}H NMR (DMSO-d_6) δ: 10.22 (s, 1H, NH), 9.02 (s, 1H, OH), 6.82—7.90 (m, 8H, ArH), 2.31 (s, 3H, CH_3); IR (KBr) ν: 3400 (OH), 3256 (NH), 1643 (CO) cm^{-1}. Anal. calcd for $C_{14}H_{13}O_2N$: C 74.01, H 5.73, N 6.17; found C 74.02, H 5.75, N 6.15.

4k Yield 48.9%, m.p. 227—228 ℃; ^{1}H NMR (DMSO-d_6) δ: 9.42 (s, 1H, NH), 9.21 (s, 1H, OH), 7.21—8.10 (m, 9H, ArH), 4.30 (d, J = 7.5 Hz, 2H, CH_2); IR (KBr) ν: 3366 (OH), 3301 (NH), 1658 (CO) cm^{-1}. Anal. calcd for $C_{14}H_{13}O_2N$: C 74.01, H 5.73, N 6.17; found C 73.97, H 5.71, N 6.20.

4l Yield 50.8%, m.p. 238—239 ℃; ^{1}H NMR (DMSO-d_6) δ: 9.61 (s, 1H, NH), 8.62 (s, 1H, OH), 7.61—8.20 (m, 4H, ArH), 3.50—3.68 (m, 2H, NCH_2), 1.01—1.90 (m, 4H, $NCCH_2CH_2C$), 0.92 (t, J = 6.8 Hz, 3H, CH_3); IR (KBr) ν: 3385 (OH), 3320 (NH), 1657 (CO) cm^{-1}. Anal. calcd for $C_{11}H_{15}O_2N$: C 68.39, H 7.77, N 7.25; found C 68.35, H 7.79, N 7.22.

Results and discussion

Considering the balance between loading capacity and the solubility profile of the resulting polymer derivative, PEG of molecular weight 3400 with two hydroxy groups is choosed as the support. In the course of reaction, the PEG support solubilized the reacting center in the reaction solvent to lead to accelerate the reaction. After completion of reaction, all of the polymer-supported intermediates could be readily isolated using a general procedure of polymer precipitation with cold $(CH_3CH_2)_2O$, the unreacted materials and the by-products were removed by simple filtration and washing. All reactions involved are highly efficient in giving the desired compounds in good yields with high purity. It is worthy of noting that, compared with the various restrictions on the analysis of reaction development in solid-phase synthesis, the PEG-bound product purity was readily detectable by TLC to confirm the complete removal of the reagents in excess and the soluble by-products. The PEG-bound product configuration was readily analyzed by IR and ^{1}H NMR spectrometry to confirm the structure without following cleave-&-analyze technique. This non-destructive approach to monitor reaction progress makes LPCS method even more valuable. It is the most important that phenolic group of amide was attached to PEG through ester linkage to avoid its reaction.

Conclusion

In summary, a modified PEG has been developed for the soluble polymer-supported solution phase synthesis of *N*-substituted *p*-hydroxybenzoic amides. Modified PEGs were used as soluble polymer supports, as well as acting as mono-protective group in some steps. In each step of the sequence, the PEG-bound intermediates were purified by precipitation followed by simple filtration. The structure of PEG-bound product was readily analyzed by IR and ^{1}H NMR spectrometry without detecting the material from the support.

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