



Microwave-assisted preparation of functionalized resins for combinatorial synthesis

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Abstract—A series of functionalized resins were synthesized from Merrifield resin by virtue of microwave irradiation. A significant reduction in reaction time was achieved. This method provides a rapid transformation of functionalized resin in solid-phase synthesis. © 2001 Elsevier Science Ltd. All rights reserved.

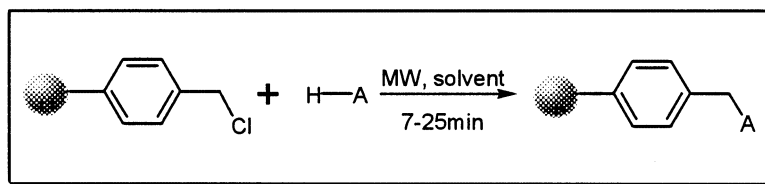
Functionalized resins enjoy a wide array of applications in chemistry. They can be used as catalysts, solid-phase synthesis supports, scavengers in parallel solution-phase synthesis, and as other polymer-supported reagents.¹ The wide adoption of combinatorial strategies in the synthesis of molecular libraries during drug discovery and screening processes has stimulated the dramatic increase in the use of solid-phase organic synthesis (SPOS).² Concomitant with the resurgence of SPOS has been the development of new polymeric supports aimed at expanding the scope of this technique.

Routinely, functionalized resins such as Wang resin, Ellman resin and SASRIN resin³ were obtained by chemical modification of preformed polymers.⁴ This methodology has been used extensively by organic chemists for years. However, the traditional method for chemical modification has many limitations. It is evident that such modifying reactions are time-consuming, as the reagents must overcome the resistance of mass transfer and steric hindrance caused by gel networks to

access the reaction sites of the preformed polymers. Most of these reactions need much longer time for complete conversion than those in homogeneous systems.

Microwave irradiation is an effective tool in enhancing reaction rates and, thus, has been widely applied.⁵ The salient features of microwave-assisted reactions lie in enhanced reaction rates, simplified manipulation and work-up, and higher purity of final products. Several reports on microwave-assisted solid-phase synthesis are currently available.⁶

We report herein a rapid and facile procedure for the preparation of functional resins as solid supports or polymeric scavengers assisted by microwave irradiation (Scheme 1). It can dramatically enhance the reaction rates over conventional methods and achieve high conversions within 7–25 min. To the best of our knowledge, it is the first report about the use of the microwave technique in this area.



Scheme 1.

Keywords: functionalisation; resins; solid-phase; microwave.

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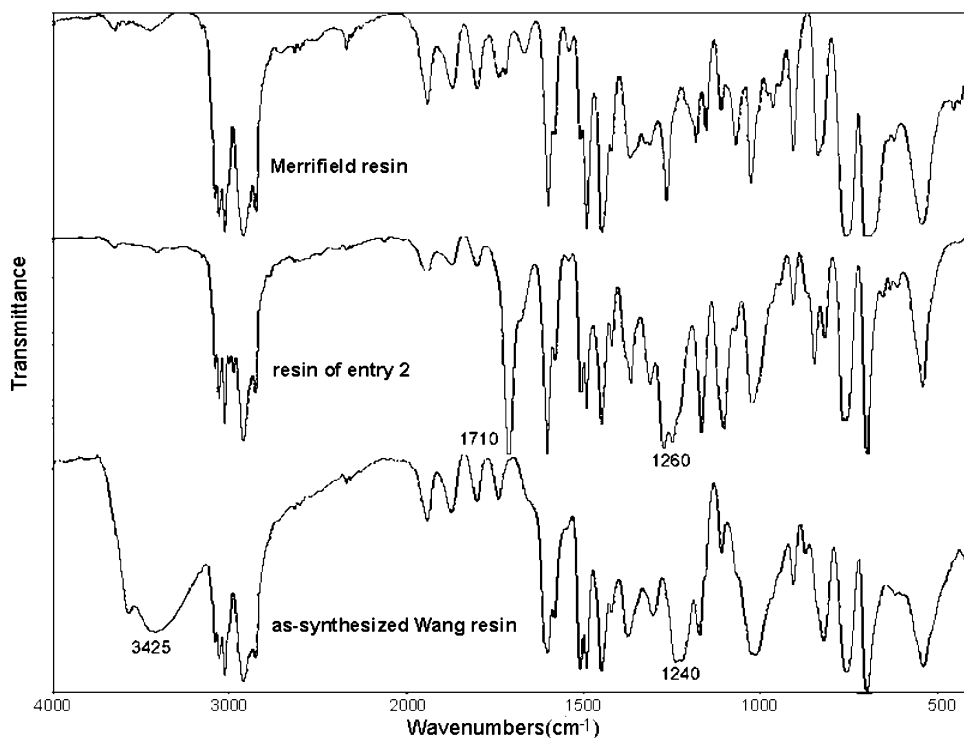


Figure 1. Illustration of reaction progress on resins by FT-IR spectra.

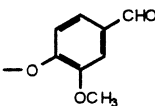
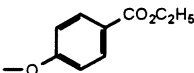
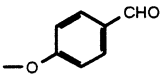
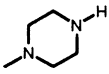


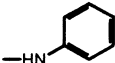
The choice of solvents is pivotal in this procedure. To improve microwave-absorption efficiencies, highly polar solvents should be selected. However, polar solvents are often poor in resin swelling and resin swelling is necessary in facilitating mobility of reactants in polymer gel networks. Therefore, in our protocol, a mixed solvent was chosen to balance between the two aspects mentioned above so satisfactory results can be obtained.

The preparation of Wang resin was chosen as the model reaction to confirm the feasibility of microwave-assisted functionalization. The precursor of Wang resin (entry 2) was prepared under microwave irradiation. Cross-linked Merrifield resin (1.15 mmol/g, 100–200 mesh) 1 g was swelled in 20 ml DMF. 2 equiv. of sodium methylate and 2 equiv. of ethyl *p*-hydroxybenzoate dissolved in 5 ml ethanol were subsequently mixed with the swelled resin and DMF. The mixture was then refluxed under microwave irradiation (100 W) for 7 min.⁷ The resin was collected by filtration and washed with 50% aqueous ethanol, acetone, CH_2Cl_2 , and methanol in succession. FT-IR analysis of the resin indicated strong characteristic absorption for ester carbonyl at 1710 cm^{-1} and aryl alkyl ether vibration at 1260 cm^{-1} (Fig. 1).⁸ In contrast, 48 h were needed to achieve similar results

using the conventional method.⁴ Finally, the resin was converted to Wang resin by conventional reduction with LiAlH_4 . Only 0.06 mmol/g of remaining Cl on the resin was detected by using Merrifield's method.⁹ Satisfactory results were also obtained in the synthesis of other resins under microwave irradiation (Table 1). The conversions in Table 1 were calculated from the different of chloride contents before and after microwave irradiation. For example, 0.37 mmol/g of remaining Cl on the resin after irradiation was obtained in entry 4 with the method (titration) developed by Merrifield.⁹ This meant that 0.753 mmol of Cl on 1.0 g of the starting resin (1.15 mmol/g) was converted to the piperazine group considering the change of the resin weight. Thus, the conversion for entry 4 was 65%. In addition, the elementary analysis of N (N, 2.07%, or 1.48 mmol/g of the resin) for the resin obtained in entry 4 was very close to that (1.45 mmol/g) by titration of remaining Cl (the error less than 3%). Also, characteristic absorptions at 1450, 1120 and 3320 cm^{-1} were observed using FT-IR.

In summary, we have developed a rapid approach to preparing functionalized resins under microwave irradiation. This method provides a convenient pathway for rapid preparation of solid-phase synthesis supports or scavengers.

Table 1. Microwave-promoted preparation of functionalized resins

Entry	A	Method ^a	Time (min)	Conversion (%) ^b	FT-IR (cm ⁻¹ , KBr) ^c
1		I	10	88	1680(s) 1270(s)
2		I	7	95	1720(s) 1260(s)
3		I	10	82	1680(s) 1270(s)
4		II	15	65	1450(m), 1120(m) 3320(w)
5		II	20	89	1450(m) 1110(m)
6		II	25	80	1450(m) 1100(m)
7		II	20	75	1450(m), 1120(m) 3250(m), 3400(m)

^a Typical procedure of method I has been described in the text.

Typical procedure of method II: To a mixture of 1.0 g (11.63 mmol) piperazine and 0.5 ml Et₃N in 20 ml of ethylene glycol monomethyl ether, 1.0 g of Merrifield resin was added. After swelling the resin for 15 min by shaking the flask, the mixture was subjected to microwave irradiation (100 w) for a period specified in Table 1. The resin was collected by filtration and washed with THF, CH₂Cl₂, dioxane and methanol (2×25 ml) in succession. After air-drying, the functionalized resin was analyzed by FT-IR.^b The conversion is based on the final and initial chloride contents.^c See the Ref. 10.

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10. Resin **1**: FT-IR: 3060s, 2930s, 2850m, 1950w, 1870w, 1800w, 1680s, 1600s, 1400m, 1270s, 1130m, 1020m, 830m, 750m, 700s. Converted loading of A1: 0.90 mmol/g; Resin **2**: FT-IR: 3060s, 2930s, 1950w, 1870w, 1800w, 1720s, 1600s, 1450m, 1380m, 1260s, 1100m, 1020m, 850w, 700s. Converted loading of A2: 0.95 mmol/g; Resin **3**: FT-IR: 3060s, 2930s, 2750w, 1950w, 1870w, 1800w, 1680s, 1600s, 1450m, 1480w, 1310w, 1270s, 1150s, 1000m, 830w, 750m, 700s. Converted loading of A3: 0.88 mmol/g; Resin **4**: FT-IR: 3320w, 3060s, 2930s, 2800m, 2760m, 1950w, 1870w, 1800w, 1750w, 1600m, 1450m, 1350m, 1120m, 1000m, 870w, 750m, 700s. Converted loading of A4: 0.73 mmol/g; Resin **5**: FT-IR: 3060s, 2930s, 2760m, 1950w, 1870w, 1800w, 1600m, 1450m, 1350m, 1110m, 850w, 750m, 700s. Converted loading of A5: 0.98 mmol/g; Resin **6**: 3060s, 2930s, 2750m, 2700w, 1950w, 1870w, 1800w, 1600m, 1450m, 1350m, 1270m, 1100m, 1000m, 850m, 750m, 700s. Converted loading of A6: 0.87 mmol/g; Resin **7**: 3400m, 3250m, 3060s, 2930s, 1950w, 1870w, 1800w, 1600s, 1475s, 1370w, 1320m, 1270w, 1170w, 1110w, 1080m, 830w, 750m, 700s. Converted loading of A7: 0.82 mmol/g.