Solid phase synthesis of aminochalcones

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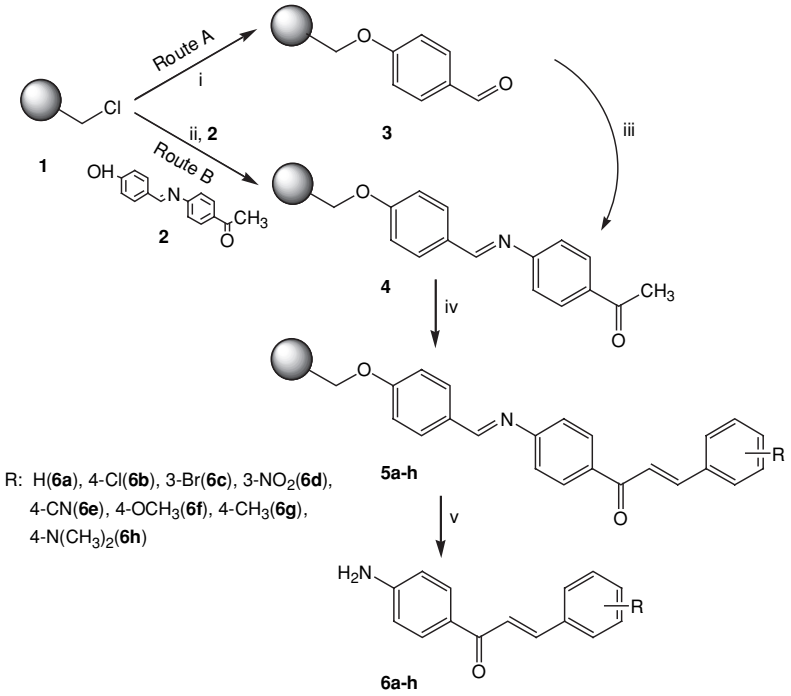
A microwave-assisted solid phase synthesis of aminochalcones via the Claisen–Schmidt condensation reaction between resin-bound *p*-aminoacetophenone and aromatic aldehydes was described.

Keywords: solid phase synthesis, aminochalcones, linker

Combinatorial chemistry is widely viewed by the pharmaceutical, agrochemical, and biotechnology industries as a key technology for accelerating the discovery of novel therapeutic agents.[1] Solid-phase organic synthesis (SPOS) is a very efficient method for production of combinatorial libraries and with the implementation of high-throughput screening for biological evaluation for hits and leads.[2] There are several advantages in solid-phase organic synthesis such as the possibility of using excess reagents, of rapid purification by filtration, for automation and so on. However, solid-phase synthesis still exhibits some shortcomings owing to the nature of the heterogeneous reaction conditions. Nonlinear kinetic behaviour, slow reactions, swelling problems, and degradation of the polymer support resulting from long reaction times are some of the problems experienced in solid-phase organic synthesis.[3] Thus, the concept of speeding up resin-bound chemistry by microwave activation (MW) has created much interest, both from the academic and industrial communities.[4]

It is a problem to transform one functional group selectively with other active groups on the same substrate left untouched under the reaction conditions. Fortunately, in solid phase organic synthesis, regioselective synthesis could be achieved through the formation of a linker by which certain active functional groups are protected.[5]

We now report the microwave-assisted solid phase organic synthesis of aminochalcones via Claisen–Schmidt condensation starting from Merrifield's resin (Scheme 1). Generally, in a homogeneous solution of *p*-aminoacetophenone and aromatic aldehydes, large amounts of by-products were obtained due to the activity of the amino group on *p*-aminoacetophenone.[6] In our approach to aminochalcones by solid-phase synthesis, a Schiff's base type linker was chosen to protect the amino group on *p*-aminoacetophenone. Two synthetic routes were investigated for the preparation of intermediate resin **4**. In route A, resin **3** was firstly prepared from Merrifield resin, *p*-hydroxybenzaldehyde and sodium methoxide in DMF under microwave irradiation using the procedure we have described previously.[7] Subsequently, **3** was reacted with *p*-aminoacetophenone under microwave irradiation to obtain **4**. However, only a moderate loading (68%) was obtained. Hence, an alternative method, route B, was investigated. In route B, Schiff's base **2** was readily synthesised by the reaction between *p*-hydroxybenzaldehyde and *p*-aminoacetophenone under microwave irradiation. Merrifield's resin was then treated with Schiff's base **2** in the presence of sodium methoxide under microwave irradiation (200W, 10 min) to afford the intermediate resin **4** (98% loading). Treating the intermediate resin **4** with various aromatic aldehydes in the presence of piperidine under microwave irradiation (200W,



Scheme 1 Microwave-assisted solid phase synthesis of aminochalcones. (i) *p*-hydroxybenzaldehyde, NaOMe, DMF, MW; (ii) Schiff's base 2, NaOMe, DMF, MW; (iii) *p*-aminoacetophenone, DMF, MW; (iv) aromatic aldehydes, piperidine, DMF, MW; (v) 10% TFA/CH_2Cl_2, r.t.

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Table 1 Microwave-assisted solid phase synthesis of aminochalcones

Entry	R	Yield/%[a]	Purity/%, HPLC	M.p./ °C/ Obs.	M.p./ °C Lit.
6a	H	73	92	109–110	102–103[8]
6b	4-Cl	74	90	189–190	193–195[9]
6c	3-Br	75	91	186–187	——
6d	3-NO_2	80	93	211–212	212–214[10]
6e	4-CN	79	93	232–233	231–233[10]
6f	4-OCH_3	67	93	149–150	148–150[10]
6g	4-CH_3	68	91	179–180	179–180[10]
6h	4-$(CH_3)_2N$	65	90	192–193	187–188[11]

[a]Isolated yields based on loading.

15min) afforded the corresponding resin-bound aminochalcones **5a–h**. In comparison, these reactions need more than 8 h to give similar results under conventional oil bath heating. Because the imine linker is labile under acidic conditions aminochalcones **6a–h** were finally cleaved from the resin **5a–h** using 10% TFA/CH_2Cl_2 for 1.5 h at room temperature. The experimental results are shown in Table 1.

In conclusion, we have developed a straightforward and efficient method for solid phase synthesis of a small library of amino chalcone derivatives under microwave irradiation. This protocol was easily adapted for the automated library synthesis.

Experimental

All reagents were purchased from commercial suppliers and used without further purification. Microwave-assisted reactions were carried out using MW-800 II apparatus.[12] Melting points were determined on a X-4 micro-melting point apparatus and are uncorrected. FTIR spectra were recorded on a Nicolet Nexus 470 IR spectrometer and ^{1}H NMR spectra were recorded on a Bruker AM 500 spectrometer with TMS as internal standard. The mass spectra were recorded on a Micromass GCT CA055 at ionising potential of 70 eV.

Preparation of Schiff base **2**: A mixture of *p*-hydroxybenzaldehyde 1.22 g (10 mmol) and *p*-aminoacetophenone 1.35 g (10 mmol) was dissolved in anhydrous acetonitrile (20 ml). The resulting solution was refluxed under microwave irradiation for 15 min. On completion, the solvent was removed *in vacuo* and the residue was crystallised from ethanol to give 2.15 g (90% yield) of desired Schiff's base **2** as yellowish crystals (m.p. 214–215 °C, lit: [13] 214.5–215 °C).

Preparation of intermediate resin **4** *(Route B)*: A mixture of Merrifield resin (1.86 mmol/g, 200-400 mesh, 2% DVB) (1.00 g), Schiff's base **2** (0.89 g, 2.0 equiv.), sodium methoxide (0.20 g, 2.0 equiv.) and DMF (20 ml) was irradiated by microwave (200 W) for 10 min. The resin was collected by filtration and washed with methanol and dichloromethane successively, until no excess reagent could be detected in the filtrate. Finally, the resins were stored under reduced pressure in a desiccator. FTIR for resin **4**: (KBr, cm^{-1}): 3074, 3020, 2920, 1690, 1630, 1600, 1500, 1450, 1320, 1260, 1150, 1000.

Determination of loading: A mixture of resin **4** (570 mg) and pyridine (4 ml) was heated at 100 °C for 1–2 h. After cooling, acetic acid (6 ml) and concentrated nitric acid (6 ml) were added, and the test tube was swirled on an ice bath for 0.5 h. The suspension was then filtered and the resin was washed with DMF (8 ml × 2). The combined filtrate was titrated with 0.1 M $AgNO_3$ and 0.1 M NH_4SCN using 40% $NH_4Fe(SO_4)_2{\cdot}12H_2O$ as an indicator. Thus, the loading can be determined by comparing the chlorine content of resin sample and starting Merrifield resin.

Preparation of resin-bound products **5a–h**: The intermediate resin **4** (1.00 g) was pre-swelled for 15 min in 10 ml of DMF and then piperidine (0.32 g, 2 equiv.) and aromatic aldehyde (2 equiv.) was added. The mixture was irradiated by microwave (200 W) for 15 min. The resins were purified by the procedure mentioned above.

Preparation of aminochalcones **6a–h**: The resin **5a–h** (1.00 g) was stirred at room temperature for 1.5 h in 20 ml of 10% TFA/CH_2Cl_2. After filtration, the resin was washed with dichloromethane (10 ml × 3) and acetonitrile (10 ml × 3), successively. The combined filtrate was concentrated and the residue was dissolved in 20 ml of dichloromethane. The resulting solution was washed with 1M NaOH saturated by NaCl (10 ml). The water layer was extracted with dichloromethane (20 ml × 3) and the solvent in the combined organic layer was removed under vacuum to give the aminochalcones **6a–h**. The structure of aminochalcones was confirmed by ^{1}H NMR, FT-IR, MS (EI), HRMS and comparison of melting points with literature values (Table 1).

Selected spectral data of aminochalcones: **6c**: IR ν_{max} (KBr, cm^{-1}): 3414, 3325, 3207, 1651, 1625, 1602, 1573, 1554, 1513, 1472, 1443, 1339, 1302, 1227, 1172; ^{1}H NMR δ_H (acetone-d_6, 500 MHz) 5.59 (s, 2 H, NH_2), 6.73 (d, J = 8.6 Hz, 2 H, CH=CH), 7.39 (t, J = 7.9 Hz, 1 H, ArH), 7.56–7.64 (m, 2 H, ArH), 7.77 (d, J = 7.9 Hz, 1 H, ArH), 7.91–8.04 (m, 4 H, ArH). MS (EI) *m/z*: 303 (M+1), 302, 301 (M-1), 275, 273, 222, 146, 120 (100), 92; HRMS (EI) calcd for $C_{15}H_{12}NOBr$ 303.0082, found 303.0065.

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