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Liquid phase synthesis of chiral quinoxalinones by microwave irradiation

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Abstract—Single mode microwave-assisted combinatorial synthesis of biologically interesting quinoxalinones is described. Chiral libraries of quinoxalinone were readily assembled utilizing S_NAr reactions, reduction and followed with concomitant cyclization under microwave irradiation. Enantiomeric 1,2,3,4-tetrahydroquinoxalinones were isolated in excellent yield and purity after cleavage.

With more and more novel biological targets discovered from chemical genetics research, there is an immediate need to develop efficient synthetic method for the preparation of small molecular entities. The application of microwave irradiation to the combinatorial chemistry becomes a powerful tool to rapid access a large compound collection. Major aim of this integrated technology is to exploit high degree of molecular diversity and high-throughput organic synthesis for a better way to discover new drugs, catalysts and materials. We are interested in microwave (MW) assisted soluble polymer reactions and library synthesis.[1] The domestic microwave oven is most popularly used in synthesis because of its low cost and ready availability. However, specially fabricated mono-mode microwave reactors provide homogeneous heating, temperature control and more importantly, improved safety features.[2]

In the family of biologically active heterocyclic templates, quinoxalinone system has its own identity. Quinoxalinone core is of interest as an important pharmacophore in numerous biologically active compounds. They are reported to possess significant biological properties[3–5] including utility as inhibitors of aldose reductase, partial agonists of γ-aminobutyric acid (GABA)/benzodiazepine receptor complex and kinase inhibitors (Fig. 1). Quinoxalinone skeleton is also used as an intermediate in designing different quinoxaline derivatives, which are shown to have antimicrobial,[6] antifungal[7] and anticancer[8] activities. Soluble polymer-supported organic synthesis is recognized as a convenient method to deliver vast number of small molecule libraries in mild reaction conditions.[9] Chemically robust polyethylene glycol (CH_3O–PEG–OH) is the soluble polymeric support where homogeneous reaction

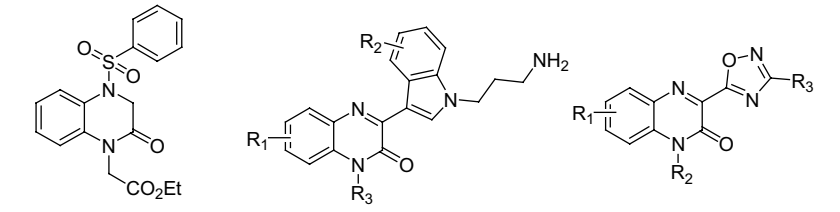

Figure 1. Biologically active quinoxalinone derivatives.

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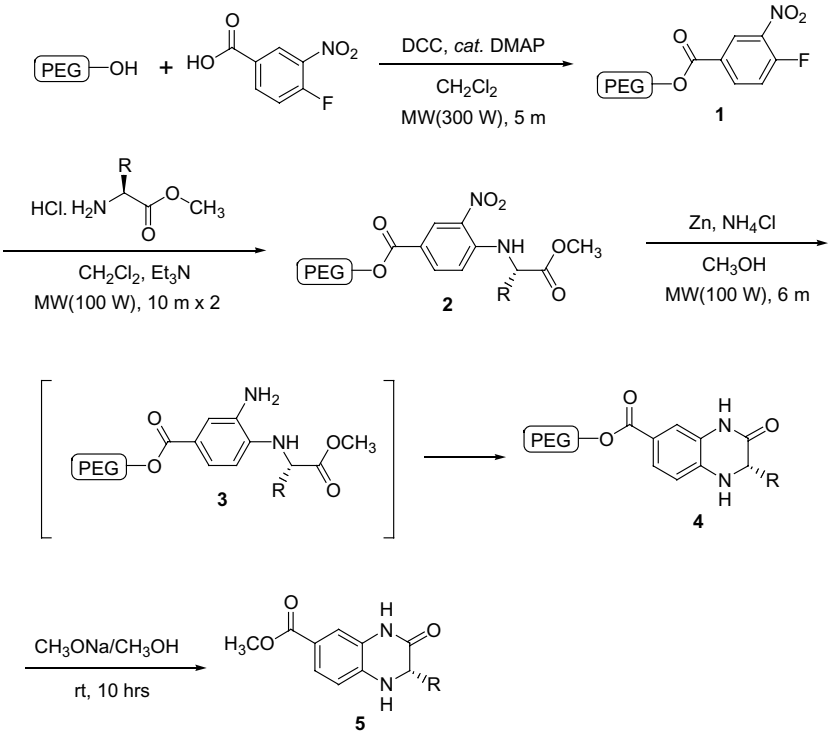
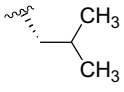
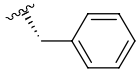
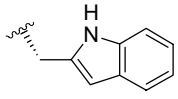
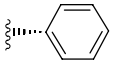
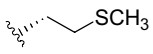


Scheme 1. Soluble polymer supported synthesis of quinoxalin-2-ones **5**.

Table 1. Rapid synthesis of quinoxalinones in microwave cavity

Entry	R	Crude yield[a]	Crude purity[b]	EI-MS
5a	H	70	73	206
5b		71	84	220
5c		74	90	248
5d		85	86	262
5e		84	77	296
5f		86	97	335
5g		99	84	282
5h		84	93	280

[a] Determined based on weight of crude sample (%).
[b] Purity determined by HPLC analysis (UV detection at $\lambda = 254$ nm) of crude product (%). Hypersil silica column, 250×4.6 mm, 5 μm.

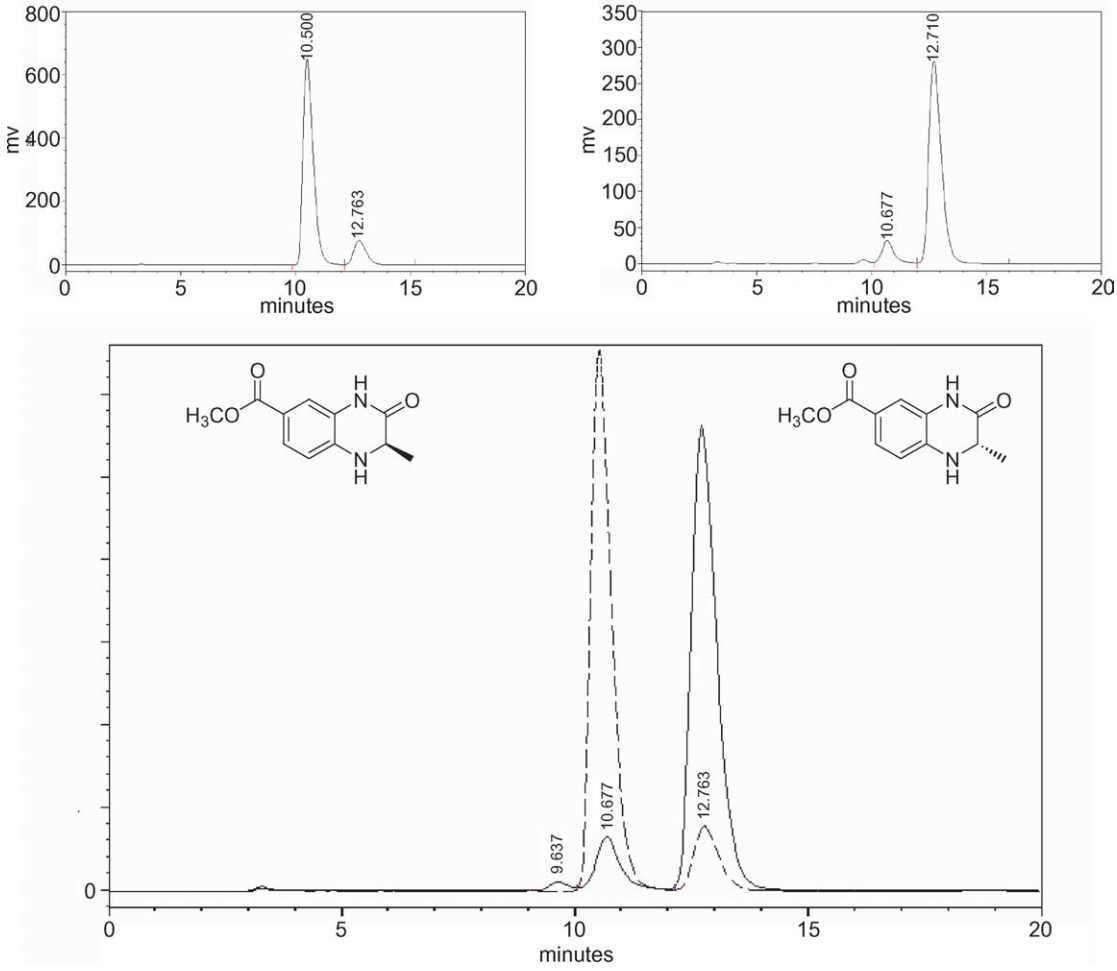


Figure 2. Chiral HPLC analysis of each enantiomer of **5b**.[†]

conditions are maintained. It is one of the inexpensive, less-toxic and recoverable polymer commonly used in the synthesis of peptides, oligosaccharides, nucleotides and other organic molecules.[9]

There are some literature evidences, which reveal the quinoxalinone synthesis on solid support[10] as well as in classical solution phase,[4] but none on liquid phase utilizing microwave to the best of our knowledge. Our synthetic method was to couple 4-fluoro-3-nitrobenzoic acid to polymer support using microwave-assisted dehydrative esterification by dicyclohexylcarbodiimide (DCC) and catalytic amount of *N*,*N*-(dimethylamino)pyridine (DMAP) in dichloromethane (Scheme 1). Reaction mixtures were precipitated in ethanol and then filtered off unreacted reagents and side products. The same work-up precipitation protocol has been followed at each step of the present reaction sequence. Proton NMR analysis clearly showed the coupling process was accomplished quantitatively in 5 min.

The resulting PEG bound *o*-fluoronitrobenzene was subjected for *ipso*-fluoro displacement with various L-α-amino acid methyl ester hydrochlorides in 10 min under microwave irradiation. The reaction was complete after double coupling with amino esters. Polymer immobilized *o*-nitrophenylamino ester **2** was treated with Zn/NH_4Cl in methanol for 6 min in a microwave cavity. It brought the quantitative reduction of nitro group followed by synchronous intramolecular cyclization to 1,2,3,4-tetrahydroquinoxalinones **4** on the support. The use of Zn/NH_4Cl is more convenient over tin(II) chloride dihydrate, which is extensively used to reduce the nitro groups bound to the insoluble polymeric support.[11] Polymer support was cleaved in CH_3ONa/MeOH solution at room temperature to give the target molecules 1,2,3,4-tetrahydroquinoxalin-2-ones **5**. Crude purities and yields of final compounds are in the ranges 73–97% and 70–99%, respectively (Table 1).

Maintenance of chiral integrity of the molecules throughout all synthetic steps could not be monitored unless the polymer support is detached. Chiral HPLC analysis of final compound **5b** after cleavage exhibited that small amount of products (~10%) underwent racemization (Fig. 2). For the quinoxalinone **5c**, around 4% racemization was observed and the bulky

[†] Determined by HPLC analysis on a chiral column-DAICEL CHIRACEL OD using *n*-hexane/2-propanol as the solvent.

quinoxalinone **5f** was isolated as optically pure without losing chirality.

In summary, we have successfully demonstrated the combination of soluble polymer supported synthesis with MW technology, providing a highly versatile platform for the generation of chiral quinoxaline-2-one libraries. The synthetic route mainly emphasizes the MW reaction conditions, simple work up procedures resulting with cleaner products. Compared with conventional thermal heating, microwave irradiation decreased the reaction time on the support from several days to several minutes. It is also worth to note that the polymer supported intermediates and polymer support itself remain stable under microwave exposure. The coupling of microwave technology with liquid-phase combinatorial synthesis constitutes a novel and attractive avenue for the rapid generation of novel biologically active compounds.

Acknowledgements

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