

# LITERATURE REVIEW: AN OVERVIEW OF MICROWAVE-ASSISTED ORGANIC SYNTHESIS USING POLYMER-SUPPORTED REAGENTS AND SCAVENGERS: PART 1

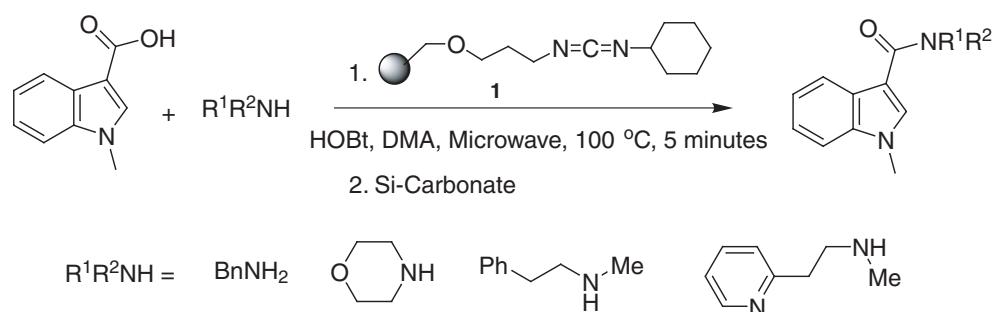
Microwave assisted organic synthesis has become an important tool to medicinal chemists for rapid organic synthesis. A huge number of research papers have appeared over the last decades on the application of microwave technology in organic synthesis.<sup>1</sup> Some of the major advantages include spectacular decrease in reaction time, improved conversions, clean product formation and wide scope for the development of new reaction conditions.

The use of polymer-supported reagents and scavengers is a powerful technique for expedited synthesis and purification.<sup>2</sup> By using polymer-supported reagents and scavengers, excess reagents and byproducts can be selectively removed by a simple filtration rather than liquid-liquid extraction and chromatographic purification. In addition, polymer-supported reagents offer further advantages that include reaction of active intermediates by "catch-and-release", selectivity and immobilization of toxic intermediates.

Rapid transformations using microwave technology has shifted the bottleneck from synthesis to the work-up and purification step. Therefore, chemists are increasingly looking for an expedited synthesis and purification strategy that would combine the use of microwave heating with polymer-assisted solution-phase organic synthesis. This overview<sup>3</sup> covers the recent literature on the significant new applications of polymer-supported reagents and scavengers using microwave heating.

## AMIDE SYNTHESIS USING PS-CARBODIIMIDE

Sauer and his group have recently reported<sup>4</sup> the application of microwave-assisted organic synthesis using the polymer-supported carbodiimide, PS-Carbodiimide **1**.<sup>5</sup> A rapid, high-yielding protocol for the synthesis of amides by the coupling of various amines and carboxylic acids in the presence of PS-Carbodiimide and microwave heating was described (Scheme 1). The reaction was complete within 5 minutes at 100 °C under microwave irradiation. The scope of the protocol was evaluated using a broad range of primary, secondary and less reactive aromatic amines, and a host of carboxylic acids. The products were isolated in high yield and purity and the reaction conditions were found to be compatible with a number of organic solvents such as NMP, DMA, DME and MeCN.



Scheme 1

## SYNTHESIS OF CARBOXYLIC ESTERS USING POLYMER-SUPPORTED ISOUREAS

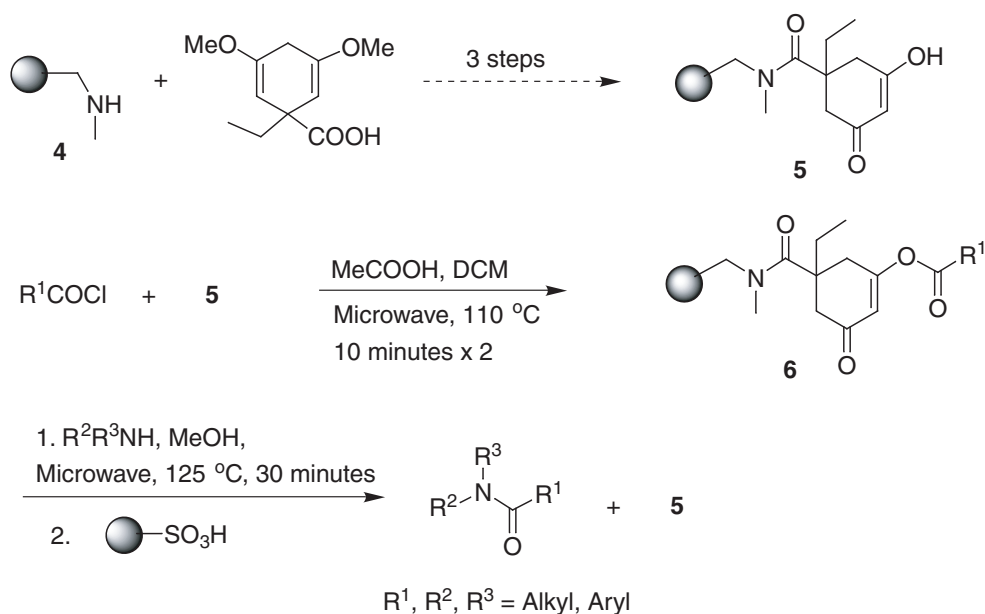
In another study, Linclau et al<sup>6</sup> have described the synthesis of a variety of carboxylic esters under microwave heating using polymer-supported isoureas **3**. The reactions were carried out in MeCN under microwave heating at 125 °C for 3 minutes. The methyl, benzyl and allyl esters of a variety of carboxylic acids have been isolated in high yield and purity (Scheme 2). The polymer-supported isoureas **3** were synthesized by Cu(II)-catalyzed reaction of a polymer-supported carbodiimide **2** with the corresponding alcohols under ambient conditions.



Scheme 2

## THREE STEP AMIDE FORMATION FROM POLYMER-SUPPORTED CYCLOHEXANE-1,3-DIONE

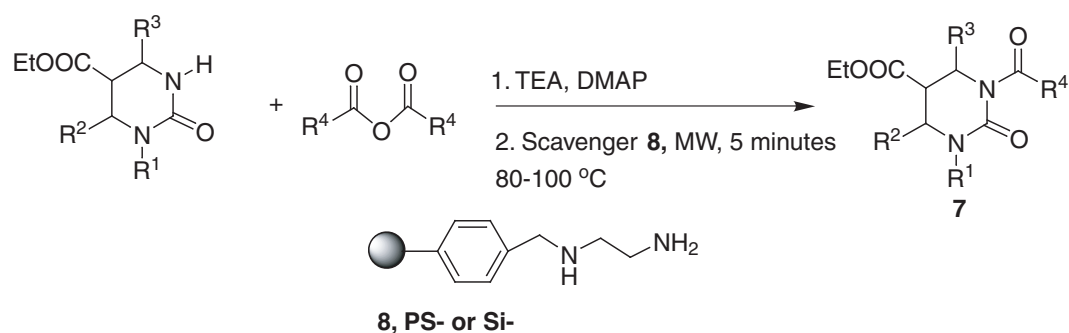
Turner and his group have reported<sup>7</sup> the synthesis of a polymer-bound cyclohexane-1,3-dione resin **5** in three steps from an aminomethyl functionalized polystyrene resin **4** (Scheme 3). The resin **5** was used for rapid synthesis of carboxamides under microwave conditions via a “capture and release” protocol. Thus, **5** was converted to the enol esters **6** which were cleaved by various amines to generate the corresponding amides in high yields.



Scheme 3

## POLYMER- AND SILICA-SUPPORTED DIAMINES FOR SCAVENGING EXCESS ACID ANHYDRIDES

Kappe and his co-workers have described<sup>8</sup> rapid purification of a small library of N-acylated dihydropyrimidines **7** by scavenging of excess acid anhydrides using both polystyrene- and silica-supported diamines **8**<sup>9</sup> under microwave irradiation (Scheme 4). The scavenging time for excess anhydrides were reduced from several hours to a few minutes under microwave heating.



Scheme 4

## REFERENCES:

1. (a) Hayes, B. L. **Microwave Synthesis: Chemistry at the Speed of Light**, CEM Publishing: Matthews, NC, **2002**; (b) Loupy, A., Ed.; **Microwaves in Organic Synthesis**; Wiley – VCH, Weinheim, **2002**; (c) Varma, R. S. **Advances in Green Chemistry: Chemical Syntheses using Microwave Irradiation**; AstraZeneca Research Foundation India, Bangalore, **2002**.
2. See for example: Bhattacharyya, S.; Rana, S.; Gooding, O. W.; Labadie, J. **Polymer-supported triacetoxyborohydride; a novel reagent of choice for reductive amination**. *Tetrahedron Lett.* 2003, 44, 4957-4960 and references 1-2 cited therein.
3. Part 2 of this review will appear in the following issue of the Newsletter.
4. Sauer, D. R.; Kalvin, D.; Phelan, K. M. **Microwave-assisted synthesis utilizing supported reagents: a rapid and efficient acylation procedure**. *Org Lett* **2003**, 5, 4721-4724.
5. PS-Carbodiimide is commercially available from Argonaut Technologies.

PS-Carbodiimide	PART NUMBER	QUANTITY
	800369	10 g
	800370	25 g
	800371	100 g
	800372	1000 g

6. Crosignani, S.; White, P. D.; Steinauer, R.; Linclau, B.: **Polymer-supported O-Benzyl and O-allylisoureas: convenient preparation and use in ester synthesis from carboxylic acids**. *Org Lett* **2003**, 5, 853-856.
7. Humphrey, C. E.; Easson, M. A. M.; Tierney, J.; Turner, N. J. **Solid-supported cyclohexane-1, 3-dione (CHD): a "capture and release" reagent for the synthesis of amides and novel scavenger resin**. *Org Lett* **2003**, 5, 849-852.
8. Dallinger, D.; Gorobets, N. Y.; Kappe, C. O. **High-throughput synthesis of N3-acylated dihydropyrimidines combining microwave-assisted synthesis and scavenging techniques**. *Org Lett* **2003**, 5, 849-852.
9. PS-Trisamine and MP-Trisamine are similar scavenger resins available from Argonaut Technologies .

PS-Trisamine	PART NUMBER	QUANTITY
	800228	10 g
	800229	25 g
	800230	100 g
	800309	1000 g

MP-Trisamine	PART NUMBER	QUANTITY
	800397	10 g
	800398	25 g
	800399	100 g
	800400	1000 g

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