

# Microwave-Promoted Hetero-Diels-Alder Reactions of 2(1H)-Pyrazinones in Ionic Liquid Doped Solvents and on Solid Support



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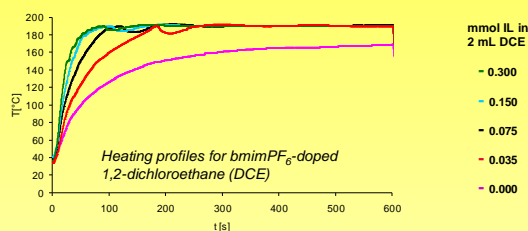
## Introduction

The readily available and broadly functionalized 2-azadiene system of the 2(1H)-pyrazinones easily undergo inter- and intramolecular Diels-Alder reactions with a wide range of dienophiles providing convenient routes to specifically substituted heterocycles. The reactions in this series are known to be rather sluggish, requiring long reaction times, high temperatures and even sometimes high pressures. Since speed is generally recognized as an important factor in high-throughput synthesis, we have explored potential rate enhancements by controlled single-mode microwave irradiation (Emrys Synthesizer) in the presence of ionic liquids. The results in solution phase were adapted to polystyrene supports using various acid labile linkers. This offers an efficient methodology for the separation of the resulting pyridines and pyridinones applying the concept of "traceless-linking". All steps in the solid-phase sequence were carried out under microwave irradiation. A detailed comparison between the microwave-assisted protocol and the conventional thermal method has been made for each reaction step.

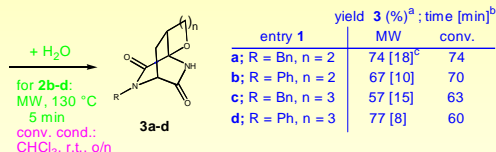
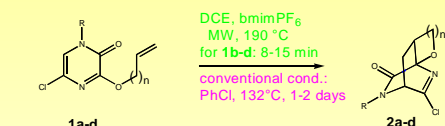
## 1 Microwave-Promoted Hetero Diels-Alder Reactions of 2(1H)-Pyrazinones in Ionic Liquid Doped Solvents<sup>1)</sup>

### Ionic Liquids (IL)-Doped Solvents:

- effectively couple with microwaves through an ionic conduction mechanism
- increase the dielectric constant of a nonpolar solvent medium

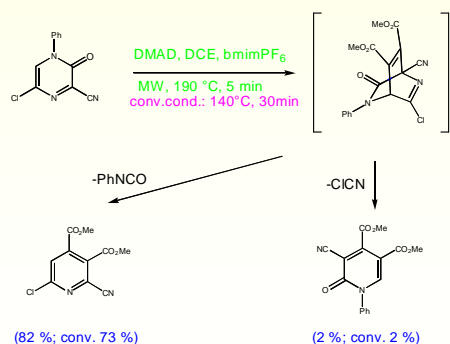


### Intramolecular Diels-Alder Reactions:



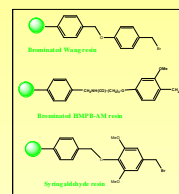
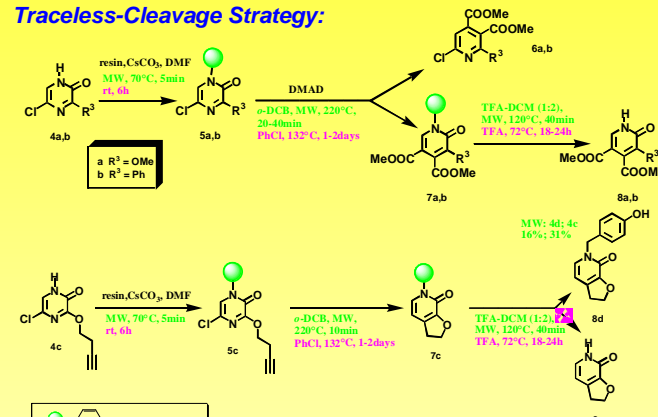
<sup>a</sup> Isolated yield of 3. <sup>b</sup> Time needed for conversion of 1 to 2.  
<sup>c</sup> Time needed for conversion of 1a to 3a as spontaneous hydrolysis of 2a occurred during the reaction.

### Intermolecular Diels-Alder Reactions:



## 2 Microwave-Promoted Hetero Diels-Alder Reactions of 2(1H)-Pyrazinones on Solid Support

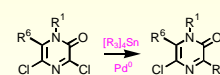
### Traceless-Cleavage Strategy:



Wang Resin		HMPB-AM Resin		Syringaldehyde Resin	
Ratio (min)	Yield (%)	Ratio (min)	Yield (%)	Ratio (min)	Yield (%)
1:2 (40)	6a (-2)	1:9 (10)	6a (-2)	5:95 (10)	6a (-2)
1:2 (40)	8a (45)	1:9 (53)	8a (45)	5:95 (10)	8a (45)
1:2 (40)	6b (53)	1:4 (27)	6b (53)	5:95 (10)	6b (53)
1:2 (40)	8b (27)	1:4 (27)	8b (27)	5:95 (10)	8b (27)
1:2 (40)	6c (31)	1:4 (20)	6c (31)	1:9 (20)	6c (31)
1:2 (40)	8d (16)	1:4 (20)	8d (16)	1:9 (20)	8d (16)

- separation of resulting pyridines **6** from pyridinones **7** applying the concept of "traceless-linking"
- the first case described in the literature where microwaves have been used for each reaction step in a solid-phase protocol
- temperatures up to 220°C do not affect stability of the PS resins!
- new tailor-made linker derived from Merrifield resin and syringaldehyde superior to Wang and HMPB-AM linkers

## 3 Microwave-Accelerated Stille Couplings of 2(1H)-Pyrazinones in Water and Organic Solvents



Pyrazinone			Yield (%)		
R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Toluene, 110°C, 3d	DMF, MW, 150W, 150°C, 5 min	H <sub>2</sub> O, MW, 300W, 150°C, 15 min
p-(OMe)Bn	Ph	H	85	94	69
	n-Bu	H	81	79	62
Bn	Ph	H	83	91	53
	n-Bu	H	81	78	58
Ph	Me	H	89	90	61
	n-Bu	H	82	80	70
Ph	Ph	p-(OMe)Ph	94	91	50
		p-(COOMe)Ph	92	85	69

## Acknowledgements

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