

The Effect Of Microwave Irradiation Towards Carbodiimide-Mediated Esterifications On Solid Phase



Alexander Stadler and C. Oliver Kappe*

Institute of Chemistry, Organic and Bioorganic Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, A-8010 Graz, Austria
email: alexander.stadler@uni-graz.at

Introduction:

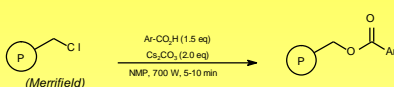
One of the most common solid-phase reactions in combinatorial synthesis involves the coupling of an acid (i.e. an amino acid) to polystyrene solid supports (i.e. Wang or Merrifield resin). A number of publications have reported the coupling of carboxylic acids to Merrifield resin via the cesium salt method and the esterification of Wang resin using carbodiimide either via the isourea method or the symmetrical anhydride method. Since the reaction times using conventional conditions have been reported to be rather long (16-48 h) we have investigated the effects of microwave irradiation towards both of these reactions using benzoic acid derivatives.

1 Microwave Equipment



Milestone MLS 1600
Multimode Batch Reactor

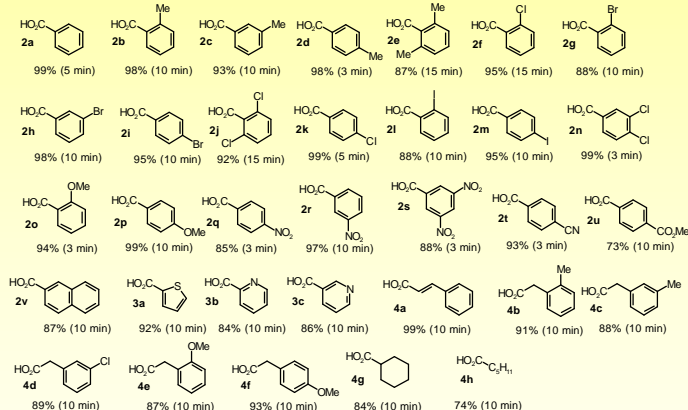
„open vessel“ system



shielded thermocouple

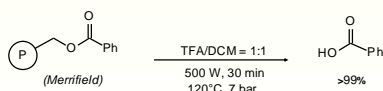
<http://www.milestonesci.com>

2 Acid Attachment to Merrifield Resin (NMP, 200°C)



Our experiments have shown that efficient attachment of carboxylic acids to chloromethylated polystyrene support is achieved by microwave flash heating in N-methylpyrrolidone (NMP) within 5-10 min.

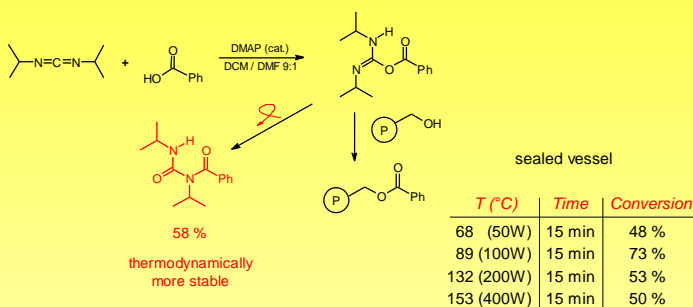
Employing microwave irradiation, acidolysis of the Merrifield linker can furthermore be carried out quantitatively using a conventional TFA/DCM mixture under elevated pressure.



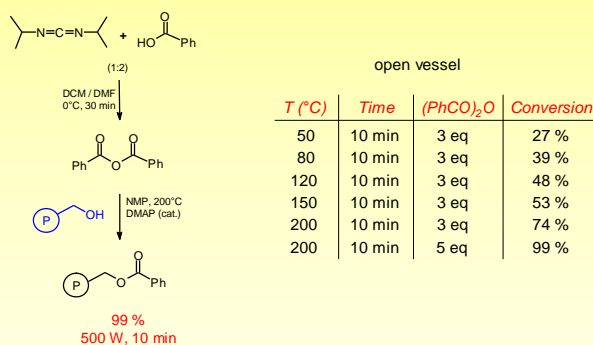
Stadler A., Kappe C.O., *Eur. J. Org. Chem.*, **2001**, 919-925

4 Esterification of Polymer-Supported Alcohol

(A) Isourea-Method



(B) Anhydride-Method



Based on earlier results, esterification of Wang resin should also be achieved more rapidly by microwave irradiation, following the standard protocols. However, during the isourea-method, rearrangement of the thermolabile intermediate into the thermodynamically stable N-acylurea is observed.

On the other hand significant rate enhancements were observed for the coupling of benzoic anhydride derivatives to polystyrene-supported alcohol using microwave flash heating in NMP. Reaction times were reduced from 2-3 days to 10 min by microwave dielectric heating.

Stadler A., Kappe C.O., *Tetrahedron*, **2001**, 3915-3920