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Microwave-Assisted Solid-Phase Ugi Four-Component Condensations

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Abstract: An 18-member library was constructed from 2 isocyanides, 3 aldehydes and 3 carboxylic acids *via* microwave-assisted solid-phase Ugi reactions on TentaGel S RAM. Products of high purity were obtained in moderate to excellent yields after reaction times of 5 minutes or less (irradiation at 60W). © 1999 Elsevier Science Ltd. All rights reserved.

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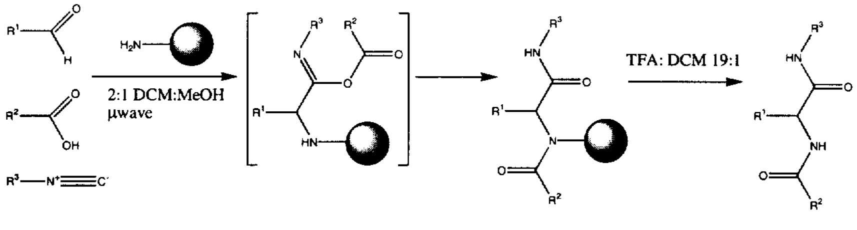
Multicomponent reactions (MCR), where three or more reactants combine to give a single product, have lately received much attention.[2] Among several useful reactions, the Ugi Four Component Condensation (U-4CC)[3] in which an amine, an aldehyde or ketone, a carboxylic acid and an isocyanide combine to yield an α-acylamino amide (see Scheme 1), is particularly interesting due to the wide range of products obtainable through variation of the starting materials.[4] Possible products include a series of known biologically active classes of compounds such as 1,4-benzodiazepine-2,5-diones,[5] diketopiperazines[6] and lactams.[7]

Furthermore, as a result of the immense number of inputs available, the U-4CC is ideal for use in the rapidly growing field of combinatorial chemistry[8] - and it was indeed for this very reaction that the potential for construction of *collections of compounds* was recognized.[9] MCRs have also proved increasingly interesting for solid-phase organic chemistry, often as elegant, simple and efficient alternatives to multi-step procedures.[10]

Even though some solution-phase Ugi reactions are known to proceed rapidly,[3b] reaction times from 24 h to several days are usually prescribed for solid-phase Ugi reactions.[4,11] Therefore, alternative strategies leading to expeditious synthesis would be very attractive for application in rapid parallel synthesis and combinatorial chemistry.



General reaction for microwave-assisted U-4CC reaction

Scheme 1

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Microwave irradiation has proved to be an efficient tool for enhancing reaction rates and has previously been used with good results in solution-phase[12] and solvent-free reactions.[13] Surprisingly, its use in solid-phase chemistry has been very limited[14,15] and the current report presents, to our knowledge, the first microwave-assisted solid-phase MCRs. Encouraged by initial experiments with irradiation of solution-phase reactions (data not shown) we have investigated the possibilities of speeding up solid-phase U-4CCs.

While any of the four components can be attached to the solid-phase,[11,16] we have initially worked solely with amino-functionalized resin. Polyethylene glycol (PEG) grafted polystyrene has previously been shown to withstand microwave irradiation[14] and was therefore chosen as the preferred resin.

A mixture of dichloromethane and methanol (DCM:MeOH, 2:1), which at the same time absorbs microwave energy[17] and solvates the resin[18] appropriately, was used as solvent for the reaction. An array of experiments carried out with different powers of irradiation revealed that optimal results were obtained at 60W.[19] However, even at 100W no byproducts were produced according to analytical HPLC.

The aldehydes, cyclohexanecarboxaldehyde (**A**), isobutyraldehyde (**B**) and benzaldehyde (**C**), and the carboxylic acids, cyclohexanecarboxylic acid (**a**), propionic acid (**b**) and benzoic acid (**c**), were chosen to test aliphatic *vs.* aromatic substituents as well as sensitivity to various steric factors. The isocyanides, cyclohexane isocyanide (**1**) and 2-morpholinoethyl isocyanide (**2**), were chosen from the relatively few commercially available isocyanides, and have both been successfully used in previous U-4CC experiments.

1	**A**	**B**	**C**
a	57%	51%	40%
b	96%	62%	48%
c	55%	76%	40%

2	**A**	**B**	**C**
a	37%	49%	24%
b	95%	60%	40%
c	28%	74%	33%

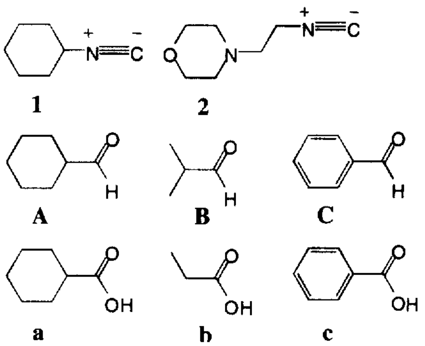

Table 1

*Yields [%] based on the support-bound amine for the three steps i) deprotection of the amine, ii) microwave-assisted four-component condensation with the carboxylic acids **a**, **b** and **c**, aldehydes **A**, **B** and **C**, and isocyanides **1** and **2**, and iii) cleavage from the resin with trifluoroacetic acid (TFA).*

An irradiation time of 5 minutes was appropriate for most reactions with **1** while reaction mixtures containing **2** seemed to absorb energy more efficiently, and therefore in most cases were irradiated for less than 5 minutes.[20]

After cleavage from the resin the yields were determined by weight. The products were verified by HPLC-MS,[21] which showed most compounds to have purities of 95% or better.[22] The preparative results are summarized in Table 1. As seen from the Table the yields are very coherent for **1** and **2**, and are comparable to what has been obtained by normal solid-phase strategies.[11]

In conclusion, we have shown that microwave irradiation is an efficient tool for enhancing reaction rates of solid-phase Ugi reactions without generating byproducts. Most likely this principle can be applied to other sluggish MCRs as well. Further studies on MCRs and microwave-assisted solid-phase synthesis are currently in progress.

General procedure for the Solid-Phase Ugi reactions: 100 mg Tentagel S RAM[23] was Fmoc deprotected with 20% piperidine in DMF, washed and transferred to a vial suitable for use in a microwave oven.[24] The resin was swelled in 250 μl (10 eq) of each of freshly made 1 M solutions of aldehyde in anhydrous DCM and carboxylic acid in anhydrous MeOH. After 30 min, 250 μl (10 eq) of a 1 M solution of isocyanide in anhydrous DCM was added,[25] an inert atmosphere established and the vial submerged into the microwave oven. After irradiation the mixture was cooled to room temperature, the resin transferred to a disposable syringe fitted with a polypropylene filter and a valve. The resin was washed extensively with DCM and MeOH and dried. The products were cleaved from the resin by 1h treatment with TFA:DCM (19:1, 1 ml), followed by wash with DCM (500 μl) and MeOH (500 μl). The solvents were evaporated and the residue was taken to complete dryness to give 2-5 mg of α-acylamino amide.[26]

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19. The model experiments were all carried out with **1Bc**. The oven used in these experiments was a Microwell 10 from Labwell AB. The oven is monomodal and can be adjusted with 1 W intervals between 1 and 500 W. **Warning! Suitable precautions must always be taken to avoid explosions due to pressure build-up. In particular, use of silicon septa as pressure relief devices is advised.**
20. All reactions with **1** were irradiated for 5 min. except **1Aa** and **1Ab** which were irradiated for 4 min 45 s. **2Aa**, **2Ab** and **2Ac** were irradiated for 4 min 45 s. **2Ba**, **2Bb** and **2Bc** were irradiated for 5 min. **2Ca**, **2Cb** and **2Cc** were irradiated for 3 min 45 s.
21. HPLC (LC-MS) were recorded on Micromass LC-Platform using Quatropole Analyzer, APcI probe (atmospheric pressure chemical ionization) and Masslynx software v.2.3 with YMC reverse-phase C-18 column 50 x 4.6 I.D., S-3 μm 120 A. Data: **1Aa**: retention time (r.t.) 8.1 min, m/z: 348; **2Aa**: r.t. 5.9 min, m/z: 379; **1Ab**: r.t. 6.7 min, m/z: 294; **2Ab**: r.t. 4.5 min, m/z: 325; **1Ac**: r.t. 6.7 min, m/z: 342; **2Ac**: r.t. 5.4 min, m/z: 373; **1Ba**: r.t. 6.3 min, m/z: 308; **2Ba**: r.t. 5.0 min, m/z: 339; **1Bb**: r.t. 5.0 min, m/z: 254; **2Bb**: r.t. 3.6 min, m/z: 385; **1Bc**: r.t. 6.0 min, m/z: 302; **2Bc**: r.t. 4.6 min, m/z: 333; **1Ca**: r.t. 6.4 min, m/z: 342; **2Ca**: r.t. 5.6 min, m/z: 373; **1Cb**: r.t. 5.5 min, m/z: 288; **2Cb**: r.t. 4.0 min, m/z: 319; **1Cc**: r.t. 6.4 min, m/z: 336; **2Cc**: r.t. 5.0 min, m/z: 367.
22. According to integrated areas recorded at $\lambda = 254$ nm. Generally α-acylamino amides with **1** as the isocyanide component were quite insoluble, whereas products obtained from **2** were more soluble. The chromatograms showed very little or no products from side reactions. In some cases small amounts of unreacted starting material were not removed completely from the resin in the washing procedure.
23. TentaGel S RAM-resin (S30 023, 0.24 mmole/g capacity) purchased from Rapp Polymere.
24. The reactions were carried out in custom made vials with a total volume of 10 ml, fitted with screw caps and 1/8 * ½ inch teflon coated silicon septa. The total volume of resin and liquid was approximately 1.5 ml, thereby allowing headspace for pressure build-up during the microwave treatment.
25. Note that most isocyanides have a very obnoxious smell! All operations should therefore be performed in fume hood!
26. When the products were cleaved off the TentaGel small amounts of PEG leaked from the resin. This has as a standard procedure been subtracted from the yield.