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Microwave-assisted synthesis of a [3+2] cycloaddition library

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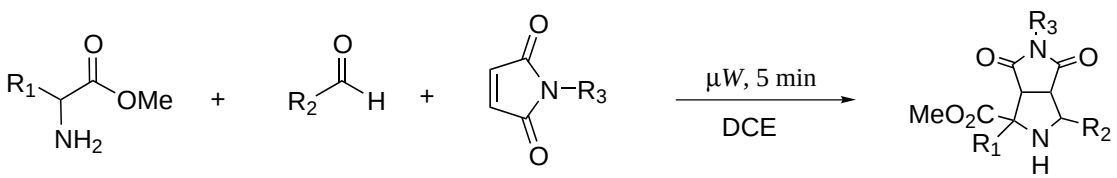
Abstract—A novel method for the synthesis of a library of substituted prolines utilizing microwave-assisted synthesis is described. The process involves rapid microwave irradiation of α-aminoesters and aldehydes to generate imines followed by the addition of a dipolarophile and subsequent irradiation to produce the [3+2] cycloadducts. The decrease in reaction time afforded by microwave irradiation allowed for the production of an 800-membered solution-phase library in twofold less time than by traditional thermal methods. These products were purified by solid-supported reagent scavenging to furnish the desired products in high yields and purity.

The generation of scaffold-based combinatorial libraries has been shown to be a valuable tool for the discovery of novel biologically relevant molecules.[1] One of the most rapid and interesting approaches to drug-like molecules is the use of multi-component condensation reactions. As an example, the use of an azomethine ylide mediated multi-component cycloaddition reaction allows for the formation of unique heterocyclic scaffolds from readily accessible starting materials. Our interest in this area stemmed from the need to produce a library of novel proline-like scaffolds driven by an informatics-based analysis of a subset of our overall compound collection.

A number of methods for azomethine ylide mediated cycloadditions are present in the literature.[2] However, the majority of these methods require either Lewis or protic acids to catalyze the cycloaddition reaction. There are reports on solid-support wherein no acid catalysis was used but reaction times were reported to range between 18 and 36 hours.[3] In addition, these reports indicate that significant decomposition of starting material and intermediates occurred due to the prolonged heating cycles required for completion. We wish to report the development of a simple, rapid, two-step, one-pot method for the conversion of α-aminoesters, aldehydes, and maleimides into corresponding pyrrolidines in good to excellent yields using single-mode microwave irradiation (noted as μW) employing a commercially available technology platform (Scheme 1).[4]

The multi-component diversity elements are introduced by simple addition of 1 equivalent of an amine to 1.1 equivalents of an aldehyde in 1,2-dichloroethane (0.25 M) and subsequent irradiation at 180°C for 2 min.[5] This is then followed by addition of the maleimide (0.85 equivalents) component via the automated pipetting features of the instrument and heating the resulting solution to 180°C for an additional 5 min. This produced the desired products in good yield and purity as determined by HPLC. Typical crude purity was between 65 and 82%. The use of a conventional (household) microwave produced unacceptable results due to



Scheme 1.

Keywords: microwave-assisted synthesis; cycloaddition combinatorial library.

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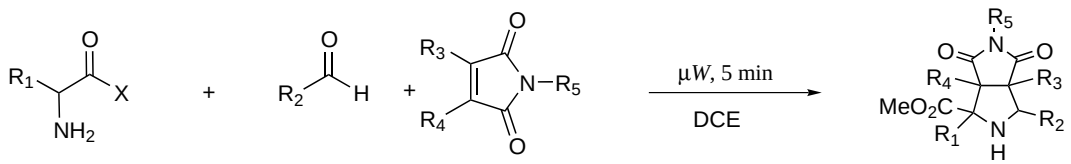
the poor absorption of microwave energy by DCE. The crude products were purified by addition of 2.5 equivalents of PS-$TsNHNH_2$ resin directly to the reaction mixture and stirring for 3 h followed by removal of the resin via filtration. The resulting products, after evaporation, showed a typical purity between 90 and 98% by LC–MS (UV and/or ELSD). This procedure proved to be optimal for a wide variety of reagents and, as with any combinatorial library, a validation of the method was performed using aldehydes, aminoesters, and maleimides that were chosen in the final design of the desired library (Table 1). The validation process was greatly accelerated since the reactions illustrated by the components listed in Table 1 were run unattended in a fully automated mode.

Limitations to this chemistry were also discovered during the validation cycle (Table 2). It was found that aromatic aldehydes formed stable imines and allowed to the subsequent cycloaddition to occur more readily, however, aliphatic aldehydes performed poorly using these conditions, possibly due to the poor stabilization of the intermediate imine or tautomerization to the undesired enamine. The poor solubility of many interesting amino acids in 1,2-DCE prevented imine formation thus limiting the diversity scope for this component of the reaction. For this reagent class it should be noted that the cycloadditions could be performed in DMF wherein the amino acid reactions produce satisfactory yield. Sterically hindered amino esters, such as phenylglycine, were also unsuccessful.

In conclusion, a library of 800 compounds was produced using the Personal Chemistry Smith Synthesizer™. LC–MS analysis of each compound verified purity and identity thus indicating that a high quality library (>75% LC–MS purity) had been produced for the screening collection. This overall streamlined strategy shows how microwave-assisted synthesis can accelerate the library development process by accelerating reaction rates or times. Furthermore, no additional catalysis (protic or Lewis acid) was needed thus simplifying purification of the products.

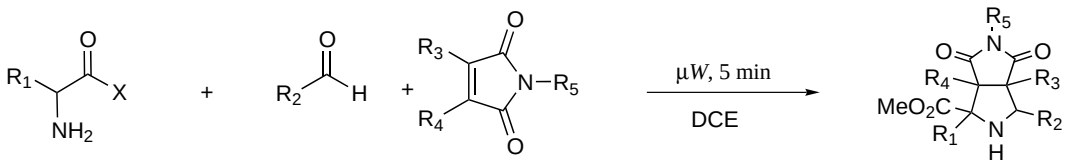
Table 1. Library validation results[a]



R1	X	R2	R3,R4	R5	Crude purity[b] (%)	Isolated yield[c] (%)
H	OCH_3	C_6H_5	H,H	$C_6H_5CH_2$	62	87
CH_3	OCH_3	4-$NO_2C_6H_4$	H,H	4-ClC_6H_4	56	82
$C_6H_5CH_2$	OCH_3	3-BrC_6H_4	CH_3, CH_3	C_6H_5	68	84
$(CH_3)_2CH$	OCH_3	2-MeC_6H_4	-C_4H_8-	4-$MeO_2CC_6H_4$	67	75
$CH_3SCH_2CH_2$	OCH_3	4-FC_6H_4	H,H	$C_6H_5CH_2$	72	89

[a] Microwave irradiation performed in a PS3 Smith Synthesizer™.
[b] Purity determined by LC–MS analysis of crude products (integration area at 254 nm) unless otherwise noted.
[c] Isolated compound after treatment with PS-$TsNHNH_2$.

Table 2. Limitations[a]



R1	X	R2	R3,R4	R5	Crude purity[b] (%)	Isolated yield[c] (%)
H	OCH_3	$CH_3CH_2CH_2$	H,H	$C_6H_5CH_2$	12	22
CH_3	OCH_3	$C_6H_5CH_2$	H,H	$C_6H_5CH_2$	17	29
4-HOC_6H_4	OCH_3	C_6H_5	H,H	$C_6H_5CH_2$	0	0
$(CH_3)_3C$	OCH_3	C_6H_5	H,H	$C_6H_5CH_2$	0	0
H	OH	C_6H_5	H,H	$C_6H_5CH_2$	0	0

[a] Microwave irradiation performed in a PS3 Smith Synthesizer™.
[b] Purity determined by LC–MS analysis of crude products (integration area at 254 nm) unless otherwise noted.
[c] Isolated compound after treatment with PS-$TsNHNH_2$.

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5. Typical experimental procedure: To 100 mg of methyl phenylalanine (0.46 mmol) was added 69 mg of *m*-anisaldehyde (0.51 mmol) in 1.84 mL of DCE (anhydrous). The solution was then capped and placed in the microwave reactor for 2 min at 180°C. Upon cooling a solution of 3,4-dimethyl phenylmaleimide 78 mg (0.39 mmol) in 0.5 mL of DCE was added at once. This solution was then heated to 180°C for an additional 5 min. Upon cooling PS-TsNHNH$_2$ 300 mg (3.25 mmol/g) was added and the solution shaken for 1 h. The solution was filtered and the filtrate concentrated in vacuo to afford the desired product.