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High-Throughput Synthesis of *N*3-Acylated Dihydropyrimidines Combining Microwave-Assisted Synthesis and Scavenging Techniques

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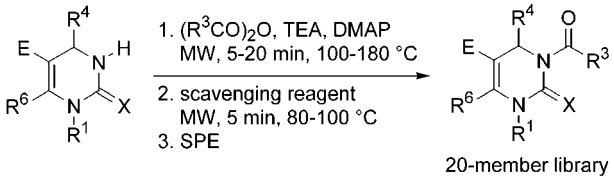
ABSTRACT



The solution-phase synthesis of *N*3-acylated dihydropyrimidines was achieved utilizing microwave flash heating both in the synthesis (acylation) and purification (scavenging) steps. Quenching times for excess anhydrides using polystyrene or silica-supported diamine sequestration reagents were reduced from several hours to minutes utilizing microwave irradiation. The use of water as sequestration agent, coupled with an efficient solid-phase extraction workup technique allowed the rapid generation of a 20-member library of *N*3-acylated dihydropyrimidines.

In the past few years, the application of microwave heating has become an important tool for enhancing combinatorial and high-throughput synthesis.[1] Successful recent high-speed microwave-assisted processes and techniques in this area include solid-phase organic synthesis,[2] the use of polymer-supported reagents,[3] synthesis on soluble polymer supports,[4] parallel processing,[5] and the construction of libraries in automated format by use of microwave/robotic technology.[6]

Surprisingly, however, there are no published reports on the utilization of microwaves in combination with supported scavenging reagents for reaction purification. This is despite the fact that the use of scavenging reagents for the selective removal of excess reagents or unwanted byproducts from a solution-phase chemical synthesis is of growing importance in the realm of high-throughput synthesis.[7] This technique offers many of the advantages of solid-supported organic

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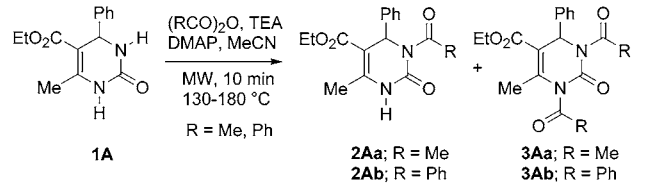
synthesis in the ease of reaction workup and product purification with the additional advantages associated with traditional solution phase synthesis.[7] Owing to the nature of the heterogeneous reaction conditions, however, most scavenging protocols require long reaction times, therefore potentially minimizing the benefits of any preceding high-speed microwave-assisted synthesis steps.

We here describe the application of controlled microwave heating for the rapid and selective scavenging of both excess reactants and unwanted byproducts in the preparation of an *N*3-acylated dihydropyrimidine library, applying both supported and unsupported nucleophilic scavenger agents.

Results and Discussion. In recent work, we have reported the solution-phase generation of a diverse library of multifunctionalized dihydropyrimidines (DHPMs) via automated robotic microwave-assisted synthesis, employing a modified Biginelli multicomponent condensation protocol.[6] Since most of the pharmacologically attractive DHPM derivatives are *N*3-acylated analogues,[8] we became interested in developing a rapid method for accessing libraries containing this structural motif in high-throughput format.

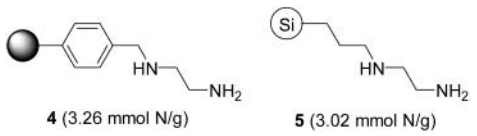
1. Microwave-Assisted Acylations. Initially, various acylation conditions involving DHPM **1A** as a model substrate and two representative anhydrides were investigated (Scheme 1). In general, these acylations are known to occur

Scheme 1



regioselectively at the more nucleophilic *N*3 position, requiring many hours of heating at high temperatures even for reactive anhydrides such as acetic anhydride.[9] After experimentation with a variety of solvents, tertiary bases, and catalysts, we quickly arrived at conditions where complete and clean conversion of the model substrate DHPM **1A** with acetic anhydride (Ac_2O) could be achieved within 10 min using microwave flash heating to 130 °C in sealed vessels (3 bar pressure). These optimized conditions involving 0.25 mmol of starting material utilized 2.5 equiv each of the anhydride and triethylamine (TEA) as base, 0.2 equiv of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) as a catalyst, and acetonitrile (0.5 mL) as solvent. For the considerably less reactive benzoic anhydride (Bz_2O), a reaction temperature of 180 °C (10 bar pressure) under otherwise identical conditions was required in order to achieve almost complete conversion (1−3% of starting material remaining) within 10 min. In contrast to the aliphatic anhydride, however, here a significant amount (ca. 12%) of the bis-acylated product **3Ab** was also formed applying these forcing conditions (only ca. 1% of bis-acetylated product **3Aa** was produced using Ac_2O at 130 °C/10 min).

2. Microwave-Assisted Scavenging. While the *N*3-acetylated DHPM **2Aa** could by isolated in near-quantitative yield and >98% purity by a simple evaporative workup, it was evident that other, less volatile anhydrides would require a more elaborate workup method to make the acylation protocol amenable to a high-throughput format. We have therefore employed the supported nucleophilic scavenging reagents **4** and **5** in our studies in order to quench excess anhydride from the reaction mixture. While the polymer-supported ethylenediamine **4** is a standard microporous cross-linked polystyrene resin that has been applied several times as a scavenging reagent for electrophiles,[7] supported ethylenediamine **5** belongs to a family of more recently introduced functionalized silica gel scavengers that are prepared from high-purity silica gel. In addition to the convenience in handling (no static charges), these materials have the advantage that they do not need to swell and therefore can be used with a variety of solvents.[10] We were particularly interested to compare the quenching capabilities of both scavengers toward anhydrides under conventional and microwave conditions in our protocol. For ease of monitoring by HPLC the acylation with Bz_2O was used as a model study.



To compare the quenching behavior of the support-bound scavengers, a number of microwave-assisted acylation runs of DHPM **1A** with Bz_2O were performed utilizing the optimized conditions described above (10 min at 180 °C). Immediately after cooling to room temperature, 3.0 equiv (based on the 0.25 mmol starting material, total N loading) of the nucleophilic amine scavengers were added as solids. The room-temperature quenching kinetics are displayed in Figure 1. Complete scavenging (no anhydride detectable by HPLC) of the remaining, unreacted 1.5 equiv of anhydride took 1−2 h for the polystyrene-based diamine **4** and 2−4 h for the silica-based diamine **5**. Note that a rather small number of functional group equivalents for anhydride sequestration was used in these experiments (ca. 2 equiv supported amine functionality per excess anhydride molecule, corresponding to an equimolar amount of diamine units). For comparison purposes (see below), the hydrolysis rate of Bz_2O achieved by addition of 10 equiv of water is also included in Figure 1 (ca. 6 h for complete conversion).

Although the scavenging experiments described above required a considerably longer period as compared to the microwave-assisted acylation step, we were delighted to

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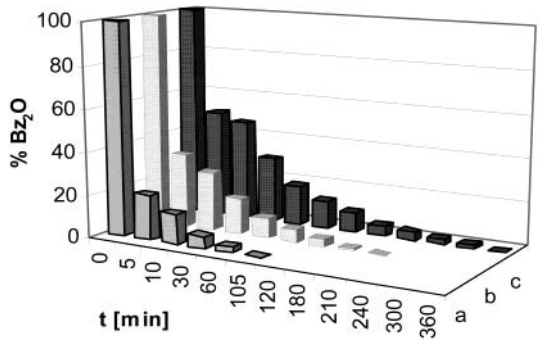


Figure 1. Kinetic analysis of excess Bz_2O sequestration after microwave-assisted benzoylation of DHPM **1A** using (a) polystyrene-supported diamine **4**, (b) silica-supported diamine **5**, and (c) water at room temperature. Data were obtained by direct HPLC analysis (280 nm) and reflect the concentration of Bz_2O at specific time intervals (t = 0, 100%).

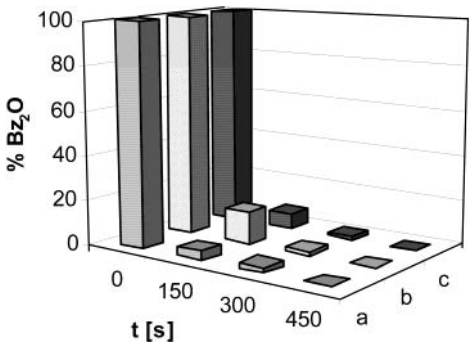


Figure 2. Kinetic analysis of excess Bz_2O sequestration using microwave heating after microwave-assisted benzoylation of DHPM **1A** using (a) polystyrene-supported diamine **4** at 80 °C, (b) silica-supported diamine **5** at 100 °C, and (c) water at 100 °C. Data were obtained by direct HPLC analysis (280 nm) and reflect the concentration of Bz_2O at specific time intervals (t = 0, 100%).

discover that all three anhydride sequestration reagents at the same time also converted the undesired bis-benzoylated DHPM **3Ab** to the *N*3-monobenzoylated product **2Ab**. This was clearly evident by HPLC monitoring showing an increase of product concentration **2Ab** at the expense of **3Ab** in the sequestration step (see Figure S1 in the Supporting Information). Among the supported scavengers, the polystyrene-bound diamine **4** and the silica-based diamine **5** were comparable in efficiency, allowing for the complete transformation **3Ab** → **2Ab** within 3−4 h.[11]

To increase the speed and effectiveness of anhydride and **3Ab** sequestration, we next performed the scavenging experiments under controlled microwave heating conditions. Microwave irradiation of the reaction mixture containing the supported scavengers (otherwise identical conditions as for the room-temperature experiments) in sealed vessels at 80−100 °C resulted in rapid and full quenching of anhydride and byproduct **3Ab** within 5−7 min depending on the scavenger used (Figure 2). For the polystyrene-supported amine **4**, 80 °C was sufficient to completely sequester both Bz_2O and the bis-acylated byproduct **3Ab**, whereas the silica-based amine **5** required 100 °C scavenging temperature. Slightly longer reaction times were needed for the complete hydrolysis of the anhydride and bis-acylated product with water (7 min, 100 °C). The application of microwave heating in the sequestration step therefore significantly reduced the required processing times from 4−6 h to 5−7 min.

3. Reaction Workup by Solid-Phase Extraction (SPE). By applying the scavenging protocols described above, the purification problem in the acylation chemistry displayed in Scheme 1 is significantly reduced since excess anhydrides and the undesired bis-acylated byproducts of type **3** can be selectively removed by suitable sequestration reagents. Apart from the solvent and TEA which are both volatile, only DMAP and the formed benzoic acid (BzOH) now need to be removed from the product. While there are several possibilities to solve or circumvent these purification issues (such as the use of resin-bound DMAP in the acylation step or the further addition of supported amines to sequester the acid) we wanted our protocol to be amenable to a high-throughput format, to be compatible with existing microwave/robotic equipment, and as cost-effective as possible.[12] Considering the fact that by simply adding a small amount of water for the hydrolysis of excess anhydride and byproduct **3Ab** essentially the same results can be achieved than by using the supported amines **4** and **5** (which both did not quench BzOH under the conditions described above) we decided to use water as a "non-supported sequestration agent" in all further experiments. Although the rate of hydrolysis Bz_2O → BzOH and **3Ab** → **2Ab** is somewhat slower as compared to the amine scavengers **4**/**5**, the use of microwave conditions minimizes this issue (7 versus 5 min). In general, 5 min of microwave scavenging proved sufficent since any remaining trace amounts of bis-acylated product were hydrolyzed during the subsequent basic SPE workup (see below). An additional advantage of employing water as scavenger—as opposed to the use of a solid reagent—is the ease with which the liquid can be introduced into the sealed microwave reaction vessel using robotic liquid dispensing.[12]

To remove BzOH and DMAP from the reaction mixture following the microwave-assisted hydrolysis ("scavenging") step, we utilized a tailor-made solid-phase extraction (SPE) cartridge. After considerable experimentation with a variety of inorganic and ion exchange materials, we discovered that the benzoylated DHPM **2Ab** could be isolated selectively

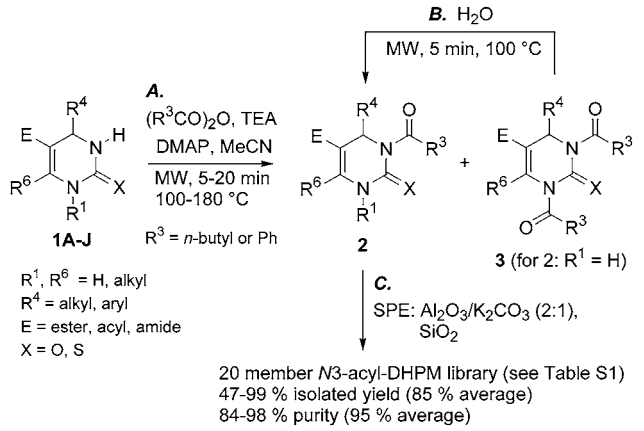
(11) The higher reactivity of the acyl group at *N*1 (in comparison to the *N*3 acyl group) can be rationalized considering the fact that the *N*1 acyl group is in conjugation with the ester functionality at C5, thereby representing a masked vinylogous triacylamine system. Bis-acylated and mixed *N*1/*N*3-acyl DHPMs can conveniently be synthesized employing the more reactive acid chlorides as acylation reagents (for details, see the Supporting Information).

(12) All microwave irradiation experiments were carried out with a dedicated single-mode instrument with integrated robotics capable of automated dispensing of liquid reagents into the microwave process vials through a septum and automated sequential microwave processing of individual reaction vials. For details, see ref 6.

from the reaction mixture by passing the solution through a short column filled with layers of basic alumina impregnated with K_2CO_3 and silica gel. Elution experiments have shown that the basic Al_2O_3/K_2CO_3 (2:1) layer retains the excess acid, whereas the acidic silica gel will retain DMAP. Best results were achieved by separating the two inorganic filtration pads by a small amount of activated carbon which was also demonstrated to adsorb minor amounts of a highly colored byproduct (for details, see the Supporting Information).

4. Application to Library Synthesis. Having protocols for the selective *N*3-benzoylation of DHPM **1A**, the rapid quenching of excess BzOH and byproduct **3Ab**, and a simple workup/purification protocol using SPE at hand we next applied and tested these procedures in the context of synthesizing a library of 20 *N*3-acylated DHPM derivatives. For this purpose, a 10-member representative subset of our previously prepared DHPM library **1A**−**J**[6] was chosen and treated with two selected anhydrides (R^3 = *n*-butyl and Ph) as outlined in Scheme 2.[13] Valerianic anhydride (R^3 = *n*-butyl) was chosen since both the anhydride and the corresponding acid could not be removed by standard evaporative techniques.

Scheme 2



(13) Detailed procedures for the all individual processing steps are provided in the Supporting Information.

In all tested cases, both the synthesis and purification strategy outlined in Scheme 2 proved successful, providing the desired *N*3-acylated DHPMs in 47−99% isolated yields and high purity (HPLC and ^{1}H NMR). The only exception were DHPMs X = S, where the corresponding *N*3-acylated derivatives could be readily synthesized but hydrolyzed under the basic SPE conditions and had to be purified by conventional silica gel chromatography or recrystallization. In one sterically demanding case (R^4 = 2,3-dichlorophenyl), it was necessary to prolong the microwave irradiation time to 20 min in order to achieve full conversion in the acylation step (see Table S1 in the Supporting Information).

In conclusion, we have demonstrated that *N*3-acylated DHPMs of type **2** can be rapidly synthesized in a high-throughput fashion by combining microwave-assisted acylations with microwave-assisted scavenging techniques. Scavenging experiments can be carried out employing either supported nucleophilic amine sequestration reagents or water. In both cases, the time required for excess anhydride quenching can be significantly reduced using microwave heating. The use of water as "non-supported nucleophilic sequestration agent", coupled with an efficient SPE purification technique, constitutes a simple and inexpensive method that can readily be automated and avoids the use of support-bound scavengers. The application and extension of this method toward the generation of larger libraries of *N*3-functionalized DHPMs utilizing other electrophiles such as acid chlorides, sulfonyl chlorides, etc. is currently under investigation.

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Supporting Information Available: Full experimental details and spectral data (NMR, HPLC, MS) for all transformations and compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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