Microwave-Assisted Solid-phase Synthesis (MASS): Parallel and Combinatorial Chemical Library Synthesis

Fahad Al-Obeidi*, Richard E. Austin, John F. Okonya and Daniel R. S. Bond

Aventis Combinatorial Technologies Center (formerly Selectide), 1580 E. Hanley Blvd, Tucson, AZ. 85737, USA

Abstract: The use of microwave technology in solid-phase organic synthesis has attracted much attention in recent years. The combination of solid support, either as a medium for chemical synthesis or as a carrier for organic reagents, with microwave heating offers several advantages over conventional techniques. Rapid and elevated heating of reaction mixtures can induce the completion of chemical transformations in minutes while several hours or days may be required for the same chemistry under conventional conditions. With decreased time of exposure to high temperatures and lessened thermal degradation, microwave accelerated chemistries often deliver products of higher purity when compared to conventional heating techniques. Several chemical syntheses on solid-phase employing microwave irradiation have been reported in the literature. The reagents, solvents, and equipment selected for microwave-mediated synthesis are important contributors to the success of the chemical transformation. Owing to the timesavings in performing chemical synthesis under microwave irradiation, the technique has become an emerging partner in solid-phase organic synthesis.

Key Words: microwave-assisted solid-phase synthesis, MASS, high-speed organic synthesis, microwave accelerated organic synthesis, solid-phase organic synthesis, microwave, combinatorial chemistry.

I. INTRODUCTION

Over the last twenty years, the methods of drug-discovery have continued to evolve. The increasing use of high-throughput biological screening (HTS) of drug candidates against pharmaceutically attractive targets has led to greater demand for large collections of drug-like chemical compounds. In addition, the progress in the human genome project has led to the discovery of a large number of new targets for drug discovery. As a consequence, there is an ever-growing demand for chemical compounds and throughput in drug discovery efforts. To meet this need, combinatorial chemistry and high-throughput synthesis in both solution-[1-7] and solid-phase have risen [4, 8-11] as primary solutions for the rapid generation of large collections of new compounds.

Parallel to the advancement of combinatorial synthesis has been the application of microwave heating to augment throughput by increasing apparent reaction rates and, accordingly, decreasing reaction times in chemical synthesis. The vast majority of reports describing microwave-assisted organic synthesis have appeared within the context of homogenous reaction mixtures or solvent-free systems [12]. The potential of microwave heating in speeding chemical synthesis was first reported in the mid-eighties [13-15]. Shortly after this pioneering work, microwave irradiation was recognized as a solution to the problem of overcoming the inherent long reaction times encountered in solid-phase synthesis. The first report on the use of microwave heating in solid-phase synthesis was by Wang and co-workers who demonstrated rate enhancement in difficult coupling reactions observed in the Merrifield [16] peptide synthesis [17]. Since this seminal report, the body of papers describing the application of microwave irradiation to enhance chemical reactions in solid-phase organic synthesis (SPOS) has steadily grown [18] and its potential to speed the synthesis of combinatorial libraries has been recognized and recently reviewed [19, 20].

Microwaves represent a segment of the electromagnetic energy spectrum that extends between 300 to 300,000 megahertz. To avoid interference with telecommunications devices and to provide optimal penetration depth, most microwave ovens operate at a frequency of 2.45 GHz. At this frequency, the energy that microwaves carry is low in relation to the energy of molecular bonds and can only affect molecular rotations. Microwave energy is thus inadequate to affect covalent bonding.

The mechanism of heating by microwave irradiation originates from the interaction between microwave active substances and microwave radiation. The electric field component of electromagnetic radiation is responsible for dielectric heating, which occurs upon microwave irradiation. At least two mechanisms for dielectric heating are operational. Dipolar polarization, occurs when polar molecules or polar substances try to align with the rapidly changing electric field of the microwave by rotation. Since the frequency of the dipole is not high enough to precisely follow the oscillating electric field, a phase difference between the orientation of the field and that of the dipole results. This phase difference causes energy to be lost from the dipole by molecular friction and collisions, giving rise to dielectric heating. The second way to transfer energy is by ionic conduction, which results if there are free ions or ions with hydrogen bonded clusters present in the substance being irradiated with microwaves. The electric field causes the ionic motion through the solution as the ions try to orient themselves along the field. These movements will result in loss of energy due to an increased collision rate, converting kinetic energy into heat. The temperature of the substance also affects conduction; as the temperature

*Address correspondence to this author at the Aventis Combinatorial Technologies Center (formerly Selectide), 1580 E. Hanley Blvd, Tucson, AZ. 85737, USA; E-mail: Fahad.Al-Obeidi@Aventis.com

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Table 1. Dielectric Constants and Boiling Points of Solvents Frequently Used in MASS*

Entry	Solvent	Dielectric Constant (ε)	Boiling Point (°C)
1	Dimethyl sulfoxide (DMSO)	47	189
2	Tetramethylene sulfone (sulfolane)	43	287
3	Dimethylacetamide (DMA)	38	166
4	1,3-Dimethylimidazolidone (DMI)	37	225
5	N-Methylpyrrolidone (NMP)	32	202
6	Dimethylformamide (DMF)	37.6	152
7	Nitrobenzene	35	211
8	Dioxane	2.2	100
9	Diphenyl ether	4	258
10	THF	NA	65
11	1,2-dichlorobenzene	9.9	179
12	Toluene	2.4	110

Data from [22] and [23] and references cited in

increases, the transfer of energy becomes more efficient. During heating of a reaction mixture in the microwave cavity both dipolar polarization and conductance could be operative in generating the heat in the reaction medium. It should be pointed out that in an alternative hypothesis, a rate enhancement seen in microwave heating has been ascribed to specific microwave effect [21].

Solvent selection is a critical consideration in the use of microwave irradiation to speed chemical transformations in SPOS. The most commonly used solid support is made from polystyrene, which is a microwave-transparent material. For this reason, to achieve heating in SPOS under microwave irradiation, the choice of reaction medium is critical. The ability of different solvents to generate heat upon exposure to microwave irradiation depends on several physical factors. In general, polar solvents with high dielectric constants (ε) generate heat at a faster rate than non-polar solvents [22]. Solvents that have been widely used in microwave-assisted solid-phase synthesis (MASS) generally possess the ability to swell the resin, dissolve the reactants, and bear a permanent dipole. Several solvents have been shown to be suitable for MASS. NMP, DMF, DMSO, methoxyethylene glycol, and 1,2-dichlorobenzene are solvents that have been commonly used (*vide infra*). Blends of microwave-inert solvents (those not bearing a net dipole) with those that are microwave active can be used as well. A collection of solvents and their related physical parameters are listed in Table 1.

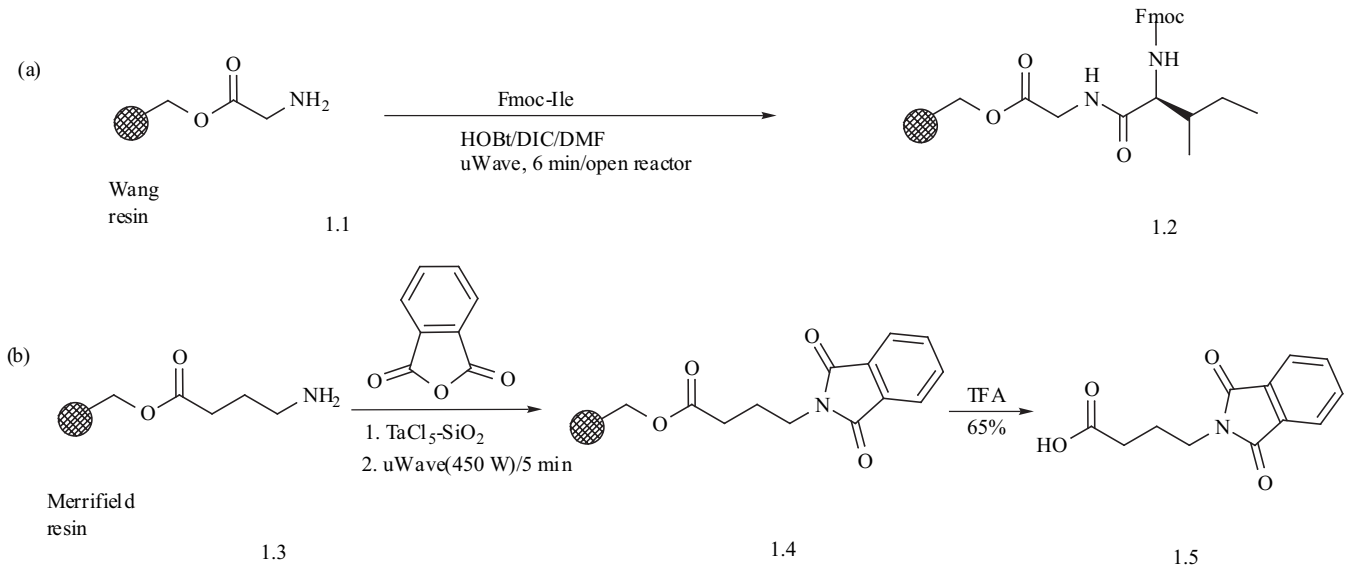
II. MICROWAVE APPLICATION IN SOLID-PHASE ORGANIC SYNTHESIS

Solid-phase reactions are typically characterized by longer reaction times compared to their solution-phase variants. Microwave dielectric heating has emerged as a powerful tool to overcome this limitation. Below, we outline the areas of SPOS chemistries that have been accelerated by microwave heating and have given satisfactory results relative to conventional protocols with exceptions in few cases (see section 5 below). We will limit our comments to examples where the primary reaction substrate was resin-bound and not address areas where microwaves were used to accelerate chemical transformations under homogenous conditions or in the presence of solid-phase reagents or scavengers. Interested readers can consult recent reviews that cover these applications. [18, 20]

1. Microwave Acceleration of Amide Bond Synthesis; Solid-Phase Synthesis of Peptides

Microwave acceleration initially attracted the attention of peptide chemists as a way to speed up the sluggish coupling of sterically hindered amino acids [17] (Scheme 1, entry **a**). This first example of the use of microwave heating in SPOS demonstrated the coupling of Fmoc-protected amino acids or peptide fragments with glycine bound to Wang resin using DMF as solvent and HOBt/DIC as the coupling reagents. The reactions were carried out in open vessels in a conventional, kitchen microwave oven for 2-6 minutes and temperature near 55 °C. The authors reported a two to four fold enhancement in coupling efficiency, especially in the case of fragment coupling.

In another example, *N*-alkyl imides were prepared from carboxylic acid anhydrides and amines under microwave heating (Scheme 1, entry **b**) [23]. Resin-bound amino acids were treated with acid anhydrides in the presence of silica gel impregnated with a Lewis acid catalyst ($TaCl_5$-SiO_2, 10 mmol percent). The solids were mixed thoroughly and heated by microwaves for 5 minutes to give greater than 50% yields of the imides. The corresponding experiment run under conventional heating (refluxing benzene for 8 h) gave only a 30% yield of the phthalic imide **1.5**. This is an



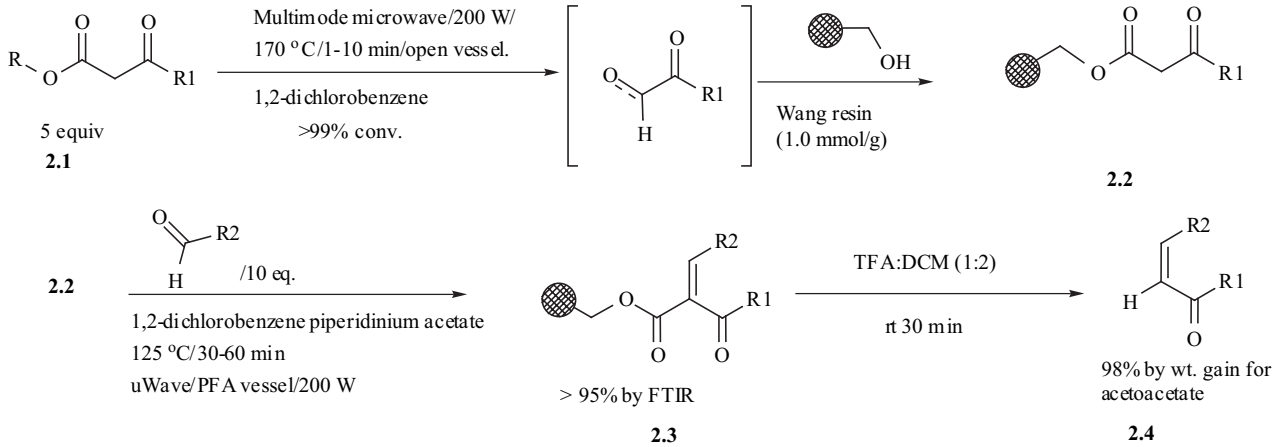
Other amino acids used: $NH_2(CH_2)_3COOH$
Other anhydrides: Phthalic, Maleic, Succinic
Microwave Oven: BPL SANYO (600 W) domestic microwave

Scheme 1.

example of a solvent-free microwave experiment. In this trial SPOS is run in the presence of an inorganic solid support as a catalyst and heating medium.

2. Microwave-Assisted Solid-Phase Synthesis of Esters; Synthesis of β-Ketoacids and Benzoic Acid Esters of Wang Resin

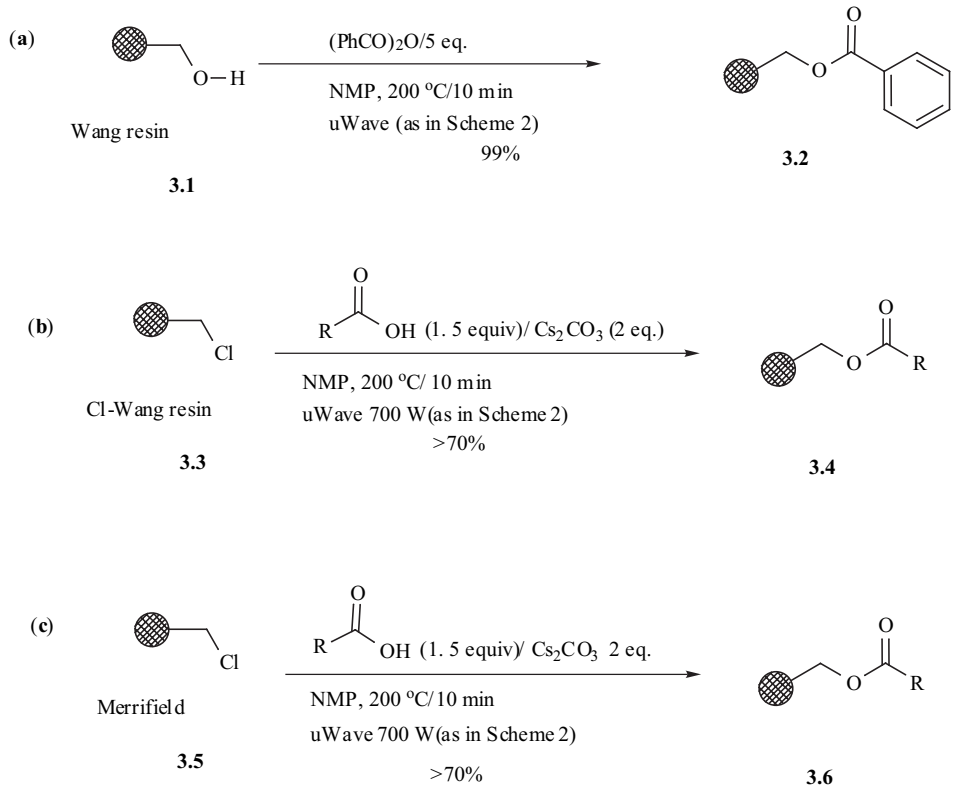
Transesterification of various β-keto esters onto Wang resin has been achieved under microwave heating (Scheme 2) [24]. Heating a mixture of Wang resin and 5 equivalents of an appropriate β-keto ester in 1,2-dichlorobenzene at 200 W and 170 °C for 10 minutes gave nearly quantitative formation of the resin bound β-keto ester. The progress of the reaction was monitored by on bead FT-IR analysis or by acidic cleavage of a small sample of the washed and dried resin. Under conventional heating, loading of the β-keto esters to the resin usually required 110 °C for several hours. The resin-bound β-keto esters (7 variants) were reacted with thirteen aldehydes under Knoevenagal condensation conditions employing microwaves as the source of heat. In all cases, the Knoevenagel condensations went to more than 95% completion. The results were confirmed by on-bead FT-IR analysis, gravimetric measurement of the washed and dried resin, and analysis of cleaved products using GC-MS and ^{1}H NMR. Using *m*-nitrobenzaldehyde as a test case, a complete conversion to product was achieved within 30-60 min, which compares favorably to reaction times of 1-2 days under conventional heating. The enhanced rate was attributed to more efficient heating and increased reaction temperature. In both the microwave and conventional cases, the outcome



R = Me, Et, or *t*-Bu
R1 = Me, Et, *i*-Pr, Bu, $ClCH_2$, Ph, Ph(4-F)
R2 = 13 arylaldehydes e.g. Ph, Ph(3-NO_2),....etc.

MW oven (Milestone MLS/ETHOS 1600 Reactor)

Scheme 2.



Scheme 3.

of the Knoevenagal condensation was virtually identical in terms of kinetics, yields, and purities of the final products **2.4**.

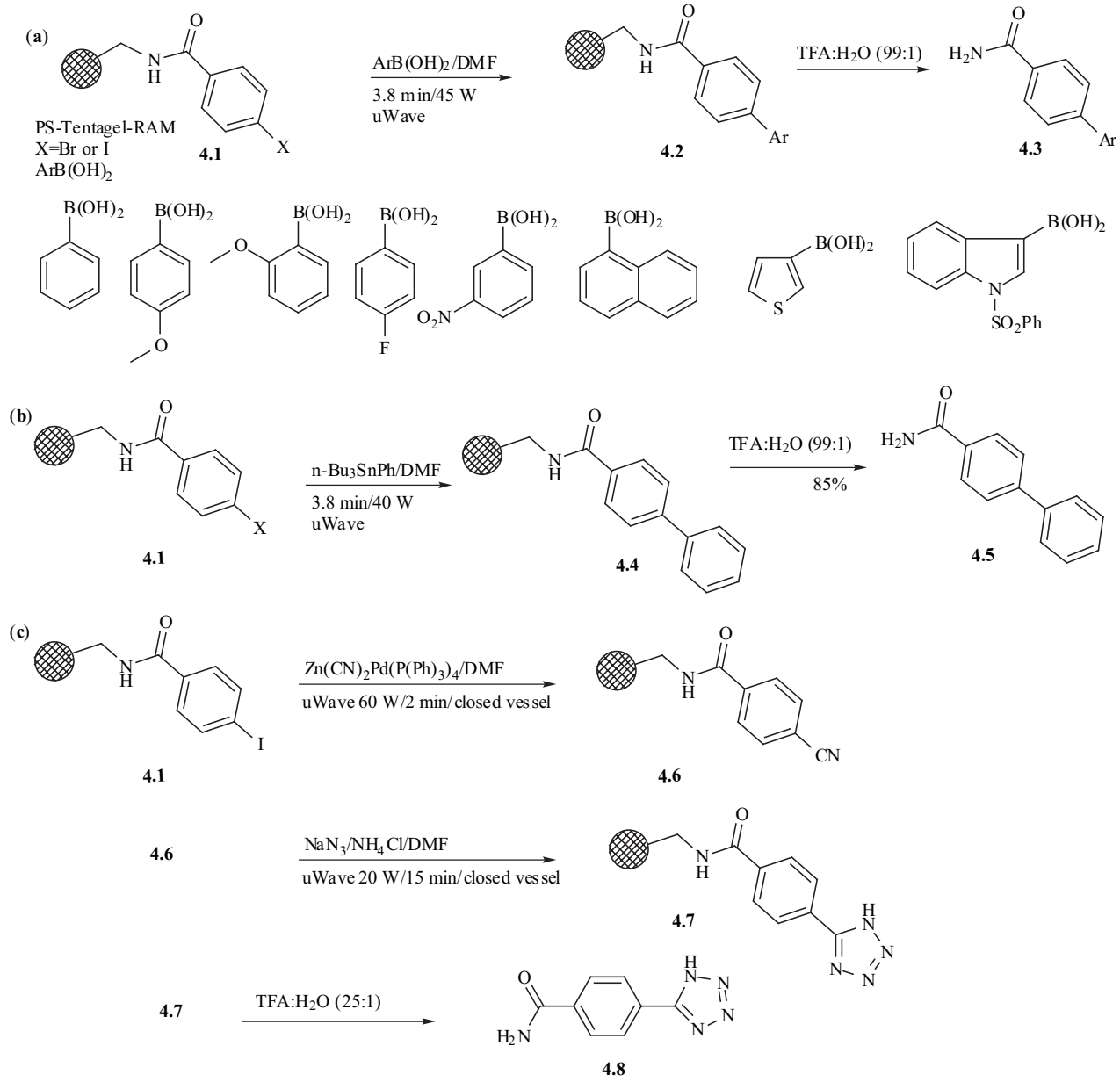
In another example, the effects of heating, solvent, number of equivalents, and coupling reagents on the loading of benzoic acid to Wang resin were studied [25]. An effort was made to define and distinguish a specific microwave effect in contrast to a thermal effect in microwave-assisted reactions. However, it was found that there was no specific microwave benefit *per se* since the efficiency of coupling under microwave irradiation was comparable with conventional heating. Owing to efficient heating, the microwave method gave a similar loading within 10 minutes compared to experiments run 2-3 days at room temperature (Scheme 3, entry **a**).

In a separate study, the esterification of aliphatic, aromatic and heterocyclic carboxylic acids with chlorinated polystyrene resins **3.3** and **3.5** (Scheme 3, entries **b** and **c)** was examined under conventional and microwave heating [26]. Thirty five acids (1.5 equivalents) were coupled to the resin in the presence of cesium carbonate (2 equivalents) in NMP with microwave heating for 10 min at 200 °C to afford **3.4** and **3.6**. The reaction was done in an open vessel equipped with a magnetic stirrer and a thermal probe to monitor the temperature. Compared to conventional heating, the results from the microwave study showed a general trend of higher loading, better purity, and shorter reaction time (200 °C for 5-15 min versus 80 °C for 12-48 h). In general, couplings went to more than 85% completion in most cases within 3-15 min under microwave heating except in the case of *p*-methylperphthalate, which went to 73% completion after 10 min.

3. Microwave-Assisted Solid-Phase Synthesis of C-C Bonds by Metal Catalyzed Cross-Coupling Reactions

Palladium-catalyzed coupling reactions represent an attractive approach for C-C bond formation suitable for combinatorial chemistry. Several applications of these reactions on solid-phase have been reviewed recently [27]. The Suzuki coupling has been demonstrated under microwave heating using a variety of boronic acids and RAM-Tentagel resin functionalized with 4-bromo- or 4-iodobenzoic acids. The reaction was performed in the presence of 2 M aqueous Na_2CO_3 and $Pd(PPh_3)_4$ utilizing a mixture of water, ethanol, and DMF as solvent [28] .The reaction mixtures were heated for about 4 min at 40-45 W power in a closed Pyrex tube that had been purged with nitrogen. The average yield was over 84% and was achieved using eight boronic acid derivatives (Scheme 4, entry **a**).

In a separate report, Stille coupling of phenyltributyltin with 4-iodobenzoylamide resin (Pd_2dba_3 and $AsPh_3$ in dry NMP) employing microwave heating for 3.8 min at 40 W gave an 85% isolated yield of **4.5** (Scheme 4, entry **b**). In an elaborate example, Pd-catalyzed cyanation of aryl and vinyl iodides on solid-phase was accomplished under microwave irradiation. The resulting aryl and vinyl nitriles were converted to their corresponding tetrazoles also by microwave heating [29]. As exemplified in scheme 4, entry **c,** conversion of iodide **4.1** to tetrazole **4.8** was achieved in two steps both of which employed microwave irradiation as the source of heat. In the first step, a mixture of resin **4.1**, $Zn(CN)_2$, and catalytic $Pd(PPh_3)_4$ in DMF was heated in a closed vessel for 2 min at 60 W. Almost complete conversion of aryl iodide **4.1** to the intermediate aryl nitrile **4.6** was seen. After cooling to room temperature, the

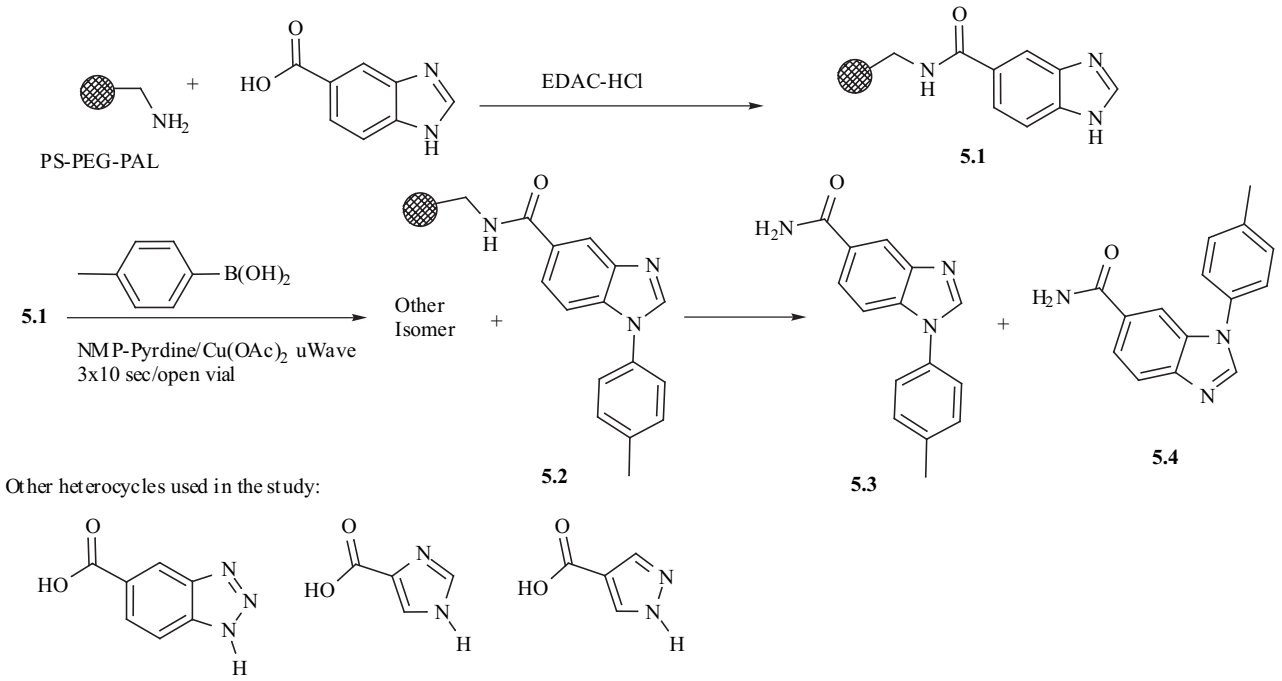


Scheme 4.

reaction vessel was opened, sodium azide and ammonium chloride were added to the resin suspension, and the reaction vessel was capped and heated at 20 W for an additional 15 min. After release of the product by trifluoroacetic acid, **4.8** was isolated in 75% yield after HPLC purification.

Under microwave irradiation, copper(II) mediated N-arylation of heterocycles has also been reported [30]. In this example, benzimidazole, imidazole, pyrazole and benzotriazole were immobilized on polystyrene-polyethylene glycol (PS-PEG) resins via the PAL-linker using EDAC.HCl as a coupling reagent (Scheme 5).

Each solid-bound heterocycle was treated with three equivalents of *p*-tolylboronic acid in presence of 5 equivalents of $Cu(OAc)_2$, molecular sieves and a 1:1 mixture of pyridine-NMP. The mixture was then heated in a loosely capped glass vial at 1000 W in a kitchen microwave oven. The heating was performed for 3x10 seconds and the resin suspension agitated manually between heating cycles. As an example, the cross-coupling of benzimidazole with *p*-tolylboronic acid under microwave acceleration was achieved in less than 5 minutes with a combined yield of 56% for two isomeric tolyl derivatives **5.3** and **5.4** with 96% purity. In comparison, under conventional heating, coupling of benzimidazole with *p*-tolylboronic acid on solid-phase required 48 h at 80 °C and provided the product in a yield of about 30% as a 1:1 mixture of the regioisomers **5.3** and **5.4**. It is interesting to point out that attempts to transfer the coupling reactions between heterocyles and boronic acid to a 96 well microtiter plate gave unsatisfactory results owing to non-uniform heating of the mixtures in the various wells. Multimode and kitchen microwave ovens usually lack homogeneity in heat distribution during microwave irradiation. Depending on the chemistry under investigation, this can sometimes result in varying levels of conversion across reaction vessels or plates.

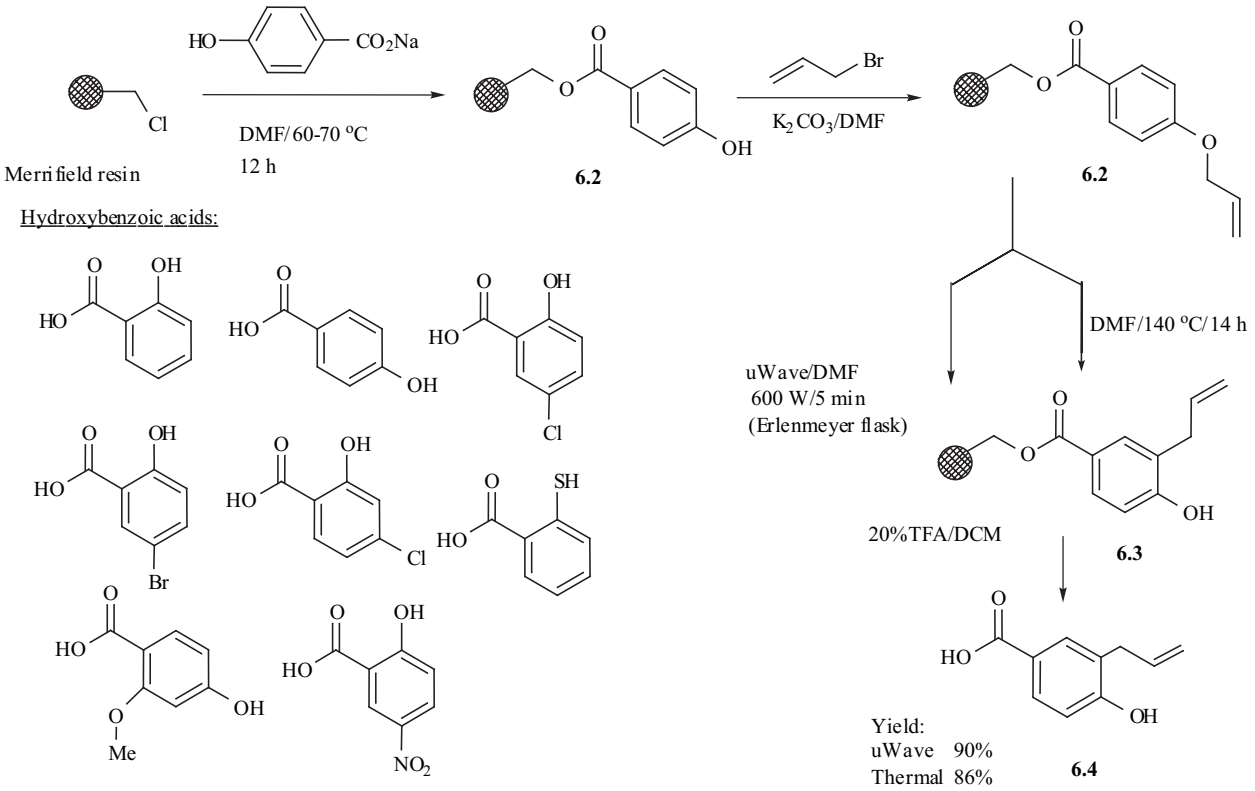


Scheme 5.

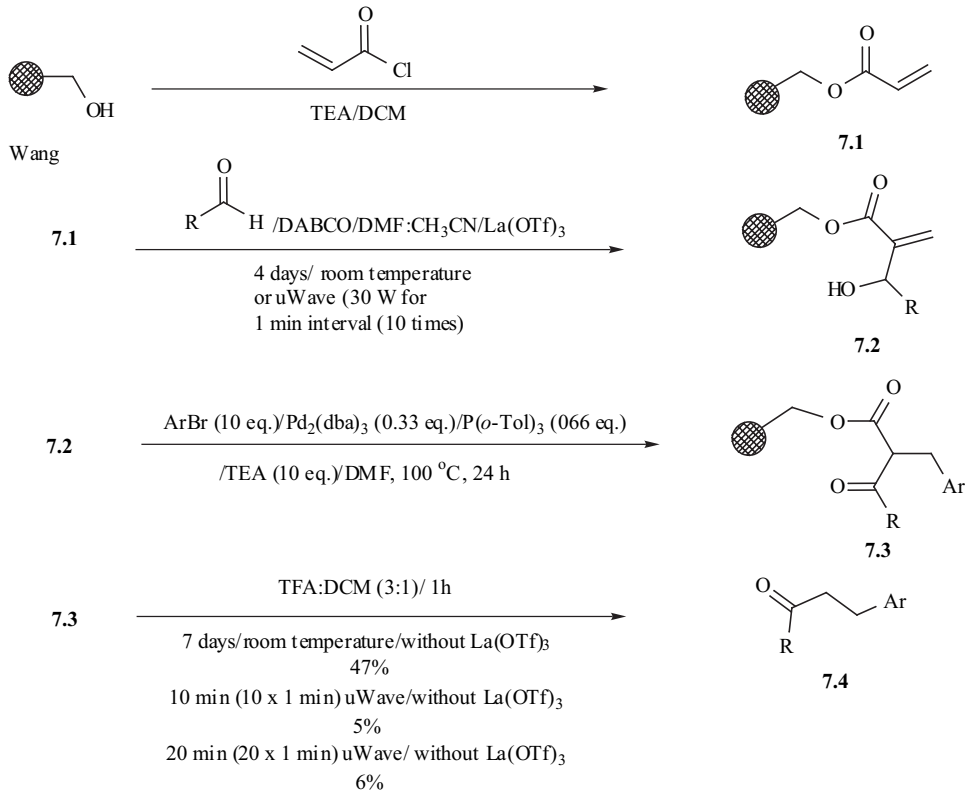
4. Microwave-assisted Claisen Rearrangement on Solid-Phase

Claisen rearrangements represent another class of important C-C bond forming reactions on solid-phase that have benefited from microwave irradiation. An example is shown in Scheme 6.

Several resin bound *O*-allylic ortho and para salicylic acids were subjected to microwave heating [31]. Eight substrate resins **6.2** were prepared from their hydroxy or thiobenzoic acid precursors and chloromethylated polystyrene resin. The functionalized resins **6.2** were reacted with allyl bromide to generate the *O*-allylic aryl ethers **6.3**. Claisen rearrangements were run in DMF under microwave



Schem 6.



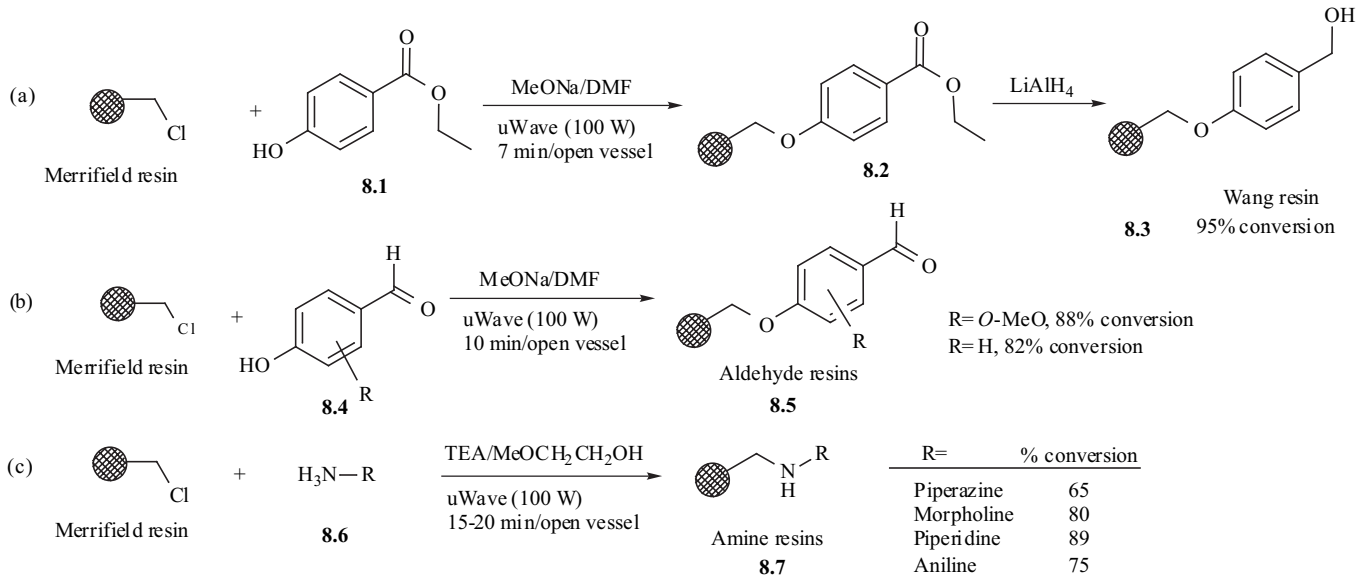
Scheme 7.

irradiation for 4-6 minutes to provide products **6.4** in greater than 68% yield. Conventional heating generated the products **6.4** in good yields (> 60%) but required heating at 140 °C for at least 10 hours.

5. Solid-Phase Synthesis of β-Keto Esters via Baylis-Hillman and Heck Reactions

One of the common applications emerging for microwave heating is the attempt to promote sluggish and problematic reactions. This was the case in the synthesis of β-keto esters by a tandem Baylis-Hillman synthesis followed by Heck Pd (0) coupling (Scheme 7) [32].

Coupling of acrylic acid to Wang resin was achieved by exposure of the resin to acryloyl chloride in presence of triethylamine in dichloromethane. Acrylate resin **7.1** was reacted with aldehyde in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) and lanthanum(III) trifluoromethanesulfonate ($La(OTf)_3$) in DMF to give the intermediate **7**. Coupling of **7.2** with an aryl bromide under Heck conditions gave **7.3**. Conventionally, the Baylis-Hillman reaction in the second step was very slow, requiring



Microwave oven -800 II multimode

Scheme 8.

4 days at room temperature. An attempt was made to improve the yield and the rate of the reaction by microwave heating. Unfortunately, heating the reaction mixture with microwaves in the presence or absence of $La(OTf)_3$ led to no improvement in the reaction.

6. Functionalization of Resins for Solid-Phase Synthesis

Solid supports can be derivatized with a linker for SPOS or functionalized to generate polymer-supported reagents (PSR). It was shown that Merrifield resin could be functionalized with chemical handles like alcohols and aldehydes or with basic groups like piperiazine or aniline [33]. The synthesis of resin with a Wang-type linker, chloromethylated polystyrene resin (Merrifield resin) in DMF/ethanol was treated with ethyl *p*-hydroxybenzoate and sodium methoxide. The suspension was refluxed by microwave (100 W) for 7 min (Scheme 8, entry **a**).

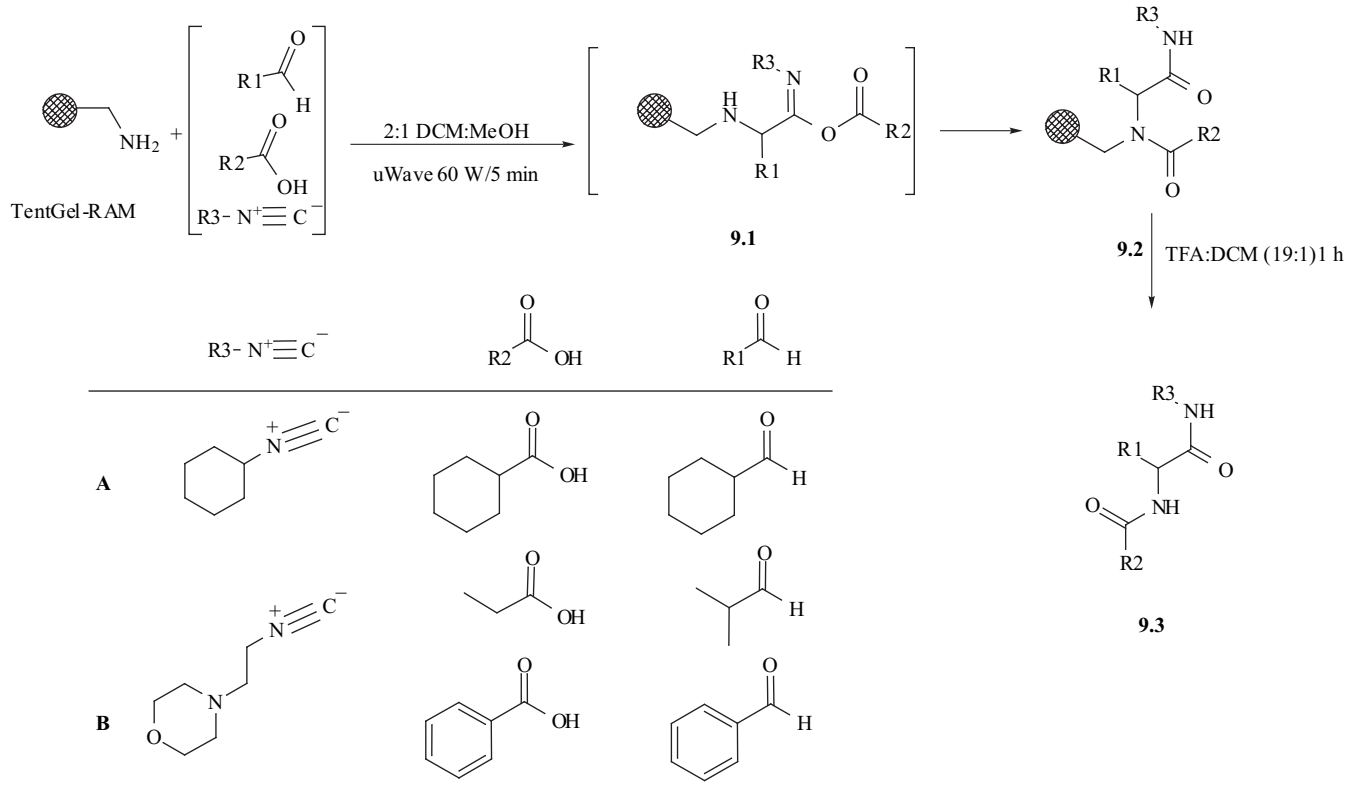
The resin was analyzed by FT-IR and then reduced with $LiAlH_4$ to give **8.3**. Analysis of the final loading indicated 95% conversion relative to the starting chloromethylated resin. Similar transformation of Merrifield resin to Wang resin under conventional heating required 48 h in DMF. Aldehyde resins **8.5** were prepared by the same microwave procedure (Scheme 8, entry **b**). Loading of amine **8.6** (Scheme 8, entry **c**) to Merrifield resin was achieved by mixing an excess of the amine with triethylamine and chloromethylated resin in ethylene glycol monomethyl ether. The mixture was heated by microwave (10 W, 15 min in the case of piperazine) to give the corresponding amine resins **8.7**. The conversion of the resin to products was monitored by FT-IR and quantified by residual chlorine analysis to give more than 60% loading.

7. Microwave-Assisted Multicomponent Condensation

Multicomponent reactions (MCR), where three or more reactants combine to give a single product, are often used in combinatorial library synthesis [34]. The Ugi 4 component condensation reaction [35] employs an amine, a carboxylic acid, an aldehyde or ketone, and an isonitrile to yield an α-acylamino amide. In the study shown in Scheme 9, two isonitriles **A** and **B** were reacted with three aldehydes and three carboxylic acids in the presence of RAM-TentaGel resin in DCM:MeOH (2:1) [36]. The reaction vials were capped under an inert atmosphere and heated for 5 min at 60 W. The final products were released from resin by acid cleavage and the yields determined gravimetrically. Recoveries ranged from 24% to 96%. The products were identified by LC-MS and most compounds showed >95% purity. In contrast, Ugi condensations under normal ambient conditions on solid-phase are known to require 24 h to several days.

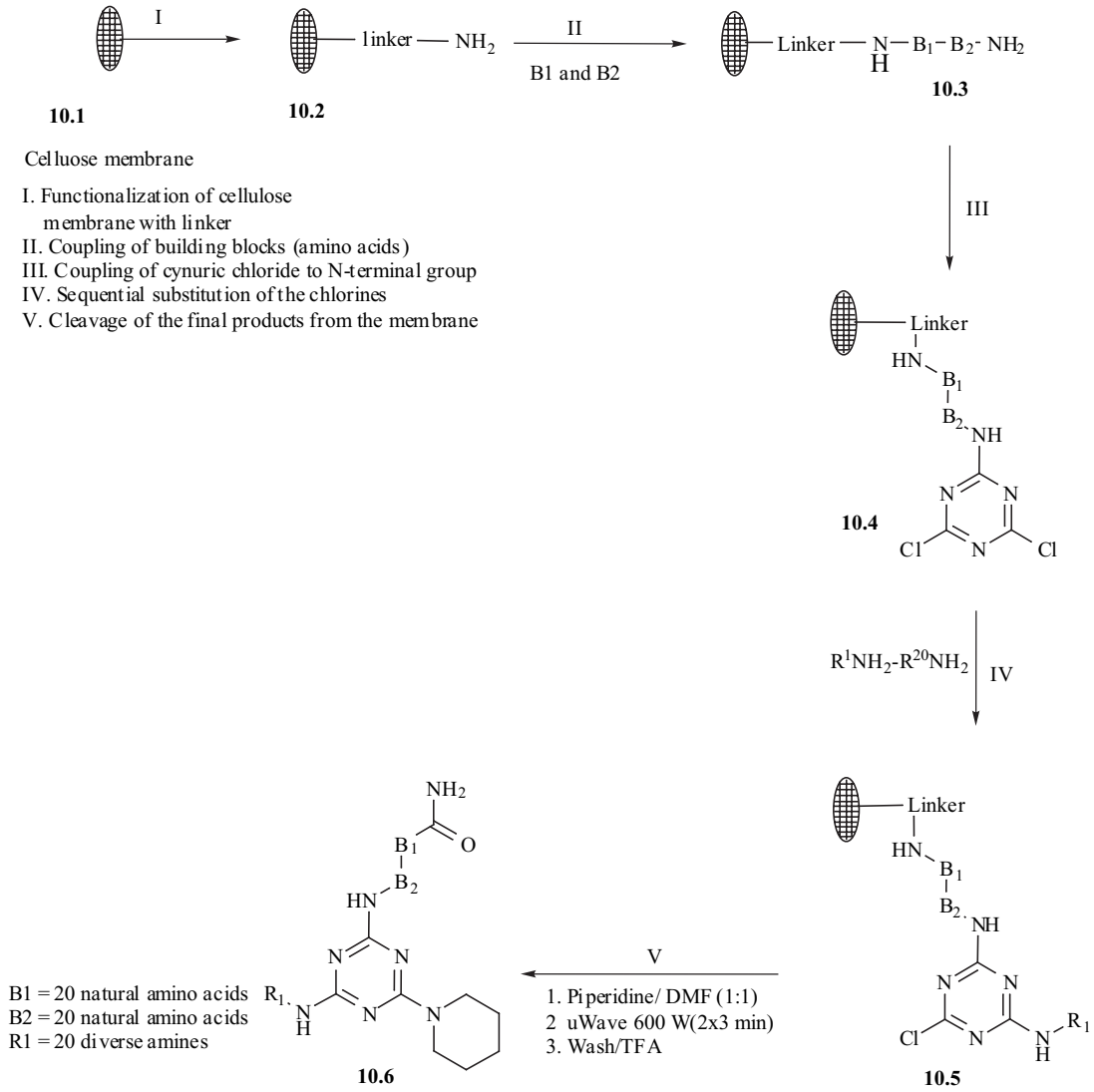
8. Microwave-Assisted Aromatic Nucleophilic Substitution on Solid-Phase

It has been recognized that microwave irradiation can enhance aromatic nucleophilic substitution (S_NAr) in solution [37]. S_NAr reactions are also known to be



Microwave oven Microwell 10 monomode (from Labwell AB). Reaction run in custom made vials (10 mL total vol.) with fitted screw caps and Teflon coated septa.

Scheme 9.



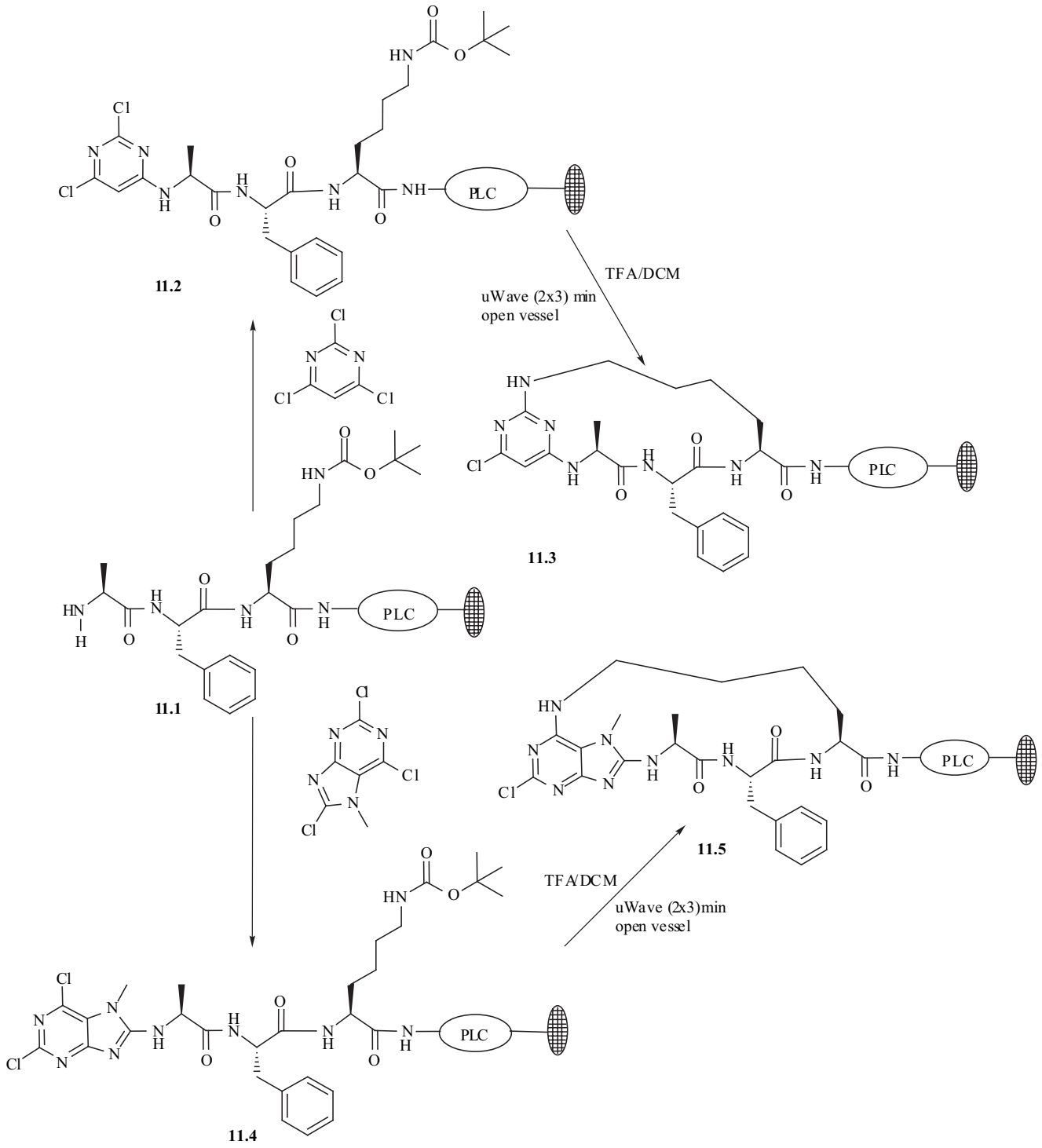
Scheme 10.

accelerated on solid-phase by microwave heating. A good example is the synthesis of an 8000-member library of dipeptides linked at the N-terminus with substituted triazine [38]. The synthesis was achieved by the initial functionalization of cellulose membrane with an amine linker on which 400 dipeptides from 20 naturally occurring amino acids were built using Fmoc synthetic strategy (Scheme 10, steps I and II).

After Fmoc-deprotection of the N-termini of the dipeptides, reaction with cyanuric chloride was performed (Step III) followed by selective substitution of one of the two remaining chlorine atoms by 20 diverse primary amines (Step IV). The third chlorine of the membrane-bound constructs, which is known to be difficult to displace, was substituted by piperidine under microwave irradiation. By microwave heating, the reaction takes only 2 x 3 minutes. The final library of dipeptide-triazines **10.6** was screened for binding of the murine IgG mab Tab2 a monoclonal antibody directly on the cellulose membrane. The same group has recently reported an interesting extension of their work by synthesis of macrocylic peptidomimetics of aromatic heterocylic-tripeptides on cellulose membrane (Scheme 11) [39].

A series of macrocyclic peptidomimetics containing pyrimidines and purines were synthesized on cellulose membranes functionalized with a photocleavable linker (PCL) using the Fmoc strategy. Microwave heating was the last step involving cyclization of heterocycle-Ala-Phe-Lys tripeptide between the second chlorine atom of the heterocycle and the N^{ε}-Lys to give **11.5**. Release of the final product was achieved by exposure of the membrane to UV light at 365 nm for 120 min on each side of the membrane.

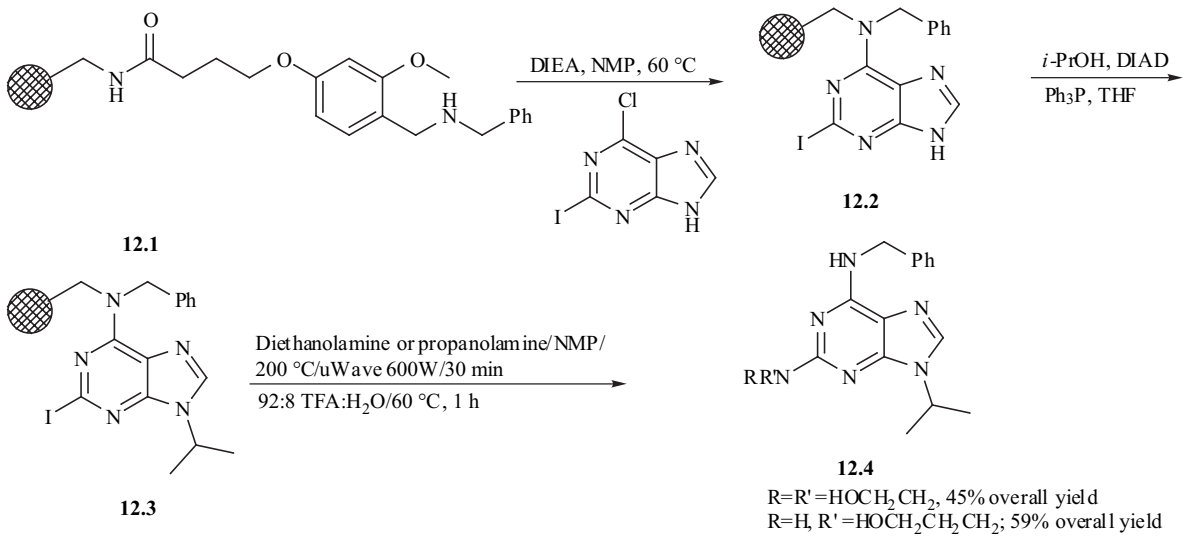
In an attempt to discover a high-throughput method for the synthesis of 2,6,9-trisubstituted purines, it was found that microwave irradiation was beneficial in accelerating the nucleophilic displacement of halogens by amines at the C-2 position of the purine nucleus. Displacement of a halogen by an amine at the C-2 position of purine derivatives typically requires high temperatures and reaction times of up to 48 hours. Through the synthesis of previously disclosed kinase inhibitors, it was demonstrated that this same type of displacement (Scheme 12, conversion of **12.3** to **12.4**) could be achieved with microwave irradiation in 30 minutes. The final products were obtained in good yields and purities [40].



Scheme 11.

III. CONCLUSIONS

Recognition of microwave-assisted solid-phase synthesis (MASS) as a powerful tool for high-throughput synthesis is growing. At the present time, lack of familiarity, instrument design and limitation in scale-up have hindered the general utility and acceptance of microwave technology. The rate enhancements that can be achieved for solid-phase reactions carried out with microwave irradiation are an attractive feature of this technology that should promote its adoption by chemists. The recent commercial availability of the necessary equipment (e.g. monomode microwave ovens, high pressure reaction vessels and automated sample handlers) have enhanced throughput and expanded the utility of microwave irradiation in solid-phase synthesis. The examples described in this review point to microwave ovens becoming an essential laboratory tool. However, further developments in microwave reaction vessel design will be necessary in order to allow this technology to merge with current state-of-the-art solid-phase synthesizers using automated resin handling. As the number of examples demonstrating the benefits of MASS increase, and with increased familiarity and improved instrument design, the



Scheme 12.

next few years should see an expansion in the use of microwave heating in drug discovery efforts.

ABBREVIATIONS

DABCO	=	1,4-diazabicyclo[2.2.2]octane
DIC	=	Diisopropylcarbodiimide
DMF	=	*N*,*N*-Dimethylformamide
DMSO	=	Dimethylsulfoxide
EDAC.HCl	=	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride
Fmoc	=	9-Fluorenylmethyloxycarbonyl
HOBt	=	Hydroxybenztriazole
HTS	=	High-throughput biological screening
IgG mab	=	Immunoglobulin G monoclonal antibody
MASS	=	Microwave-Assisted Solid-Phase Synthesis
MCR	=	Multiple Components Reaction
NMP	=	*N*-Methylpyrrolidone
PAL-Linker	=	5-[4-(aminomethyl)-3,5-dimethoxy-phenoxy]pentanoic acid
PCL	=	Photocleavable Linker
PS-PEG	=	Polystrene-polyethylene glycol
PSR	=	Polymer-supported reagents
S_NAr	=	Nucleophilic Substitution
SPOS	=	Solid-phase organic synthesis.

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