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The impact of microwave-assisted organic synthesis in drug discovery

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Microwave-assisted organic synthesis has revolutionized organic synthesis. Small molecules can be built in a fraction of the time required by classical thermal methods. As a result, this technique has rapidly gained acceptance as a valuable tool for accelerating drug discovery and development processes. This article outlines the basic principles behind microwave technology and summarizes recent trends and areas in drug discovery where this technology has made an impact.

Heating reactions with traditional equipment, such as oil baths, sand baths and heating mantles, is not only slow, it creates a hot surface on the reaction vessel where products, substrates and reagents often decompose over time. Microwave energy, in contrast, is introduced into the chemical reactor remotely and passes through the walls of the reaction vessel heating the reactants and solvents directly. Microwave dielectric heating drives chemical reactions by taking advantage of the ability of some liquids and solids to transform electromagnetic radiation into heat. A properly designed vessel allows the temperature increase to be uniform throughout the sample, leading to fewer by-products and/or product decomposition.

Microwaves entering a cavity are reflected by the walls generating 3D wave patterns within the cavity, called modes. The domestic microwave oven has a 'multi-mode' cavity, designed to have typically three to six different modes. Multi-mode cavities comprise field patterns with areas of high and low field strength, commonly referred to as 'hot and cold spots'. Consequently, the heating efficiency, especially for small loads, can vary drastically at different positions within such cavities. Furthermore, magnetrons in domestic microwave ovens are optimized for a 1000 g standard test load and, hence, operate less reliably for small loads. In spite of the inherent unreliability of such systems, early work involving microwave chemistry was performed in multi-mode ovens equipped with condensers and venting mechanisms.

Ideally, to obtain a well-defined heating pattern for small loads, a microwave apparatus with a 'single-mode' cavity, which allows only a single mode to be present, is preferred. A properly designed cavity precludes the formation of hot and cold spots within the sample, resulting in a uniform heating pattern, a factor that is very important in organic chemistry as it allows for higher reproducibility, predictability of results and hence optimization of yields. For larger loads, a well-designed multi-mode cavity equipped with power, temperature and pressure control along with the appropriate venting mechanism and safety features is suitable.

Because there are numerous reviews and books written on this topic [1–6], the scope of the current review has been restricted to a limited number of recent publications that portray the impact microwave-assisted organic synthesis (MAOS) has made, illustrated by applications in the various areas of drug discovery.

Scope of microwave-assisted organic synthesis

There are very few limitations to the types of chemistries that can be done using microwave heating. To date, the most common types of reactions that have been performed have been in the area of solution-phase synthesis, although the technique has also been used in solid-phase synthesis and is rapidly gaining popularity with solid-supported reagents and scavengers and other areas of chemistry, including polymer [7] and solid-state chemistry [8].

Solution-phase synthesis

Although the majority of reactions performed in traditional organic chemistry utilizes solvent, in microwave-assisted chemistry the use of solvents has only been recent. This is because most early MAOS was carried out exclusively in domestic microwave ovens, which

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1359-6446/06/$ – see front matter PII: S1359-6446(05)03695-0

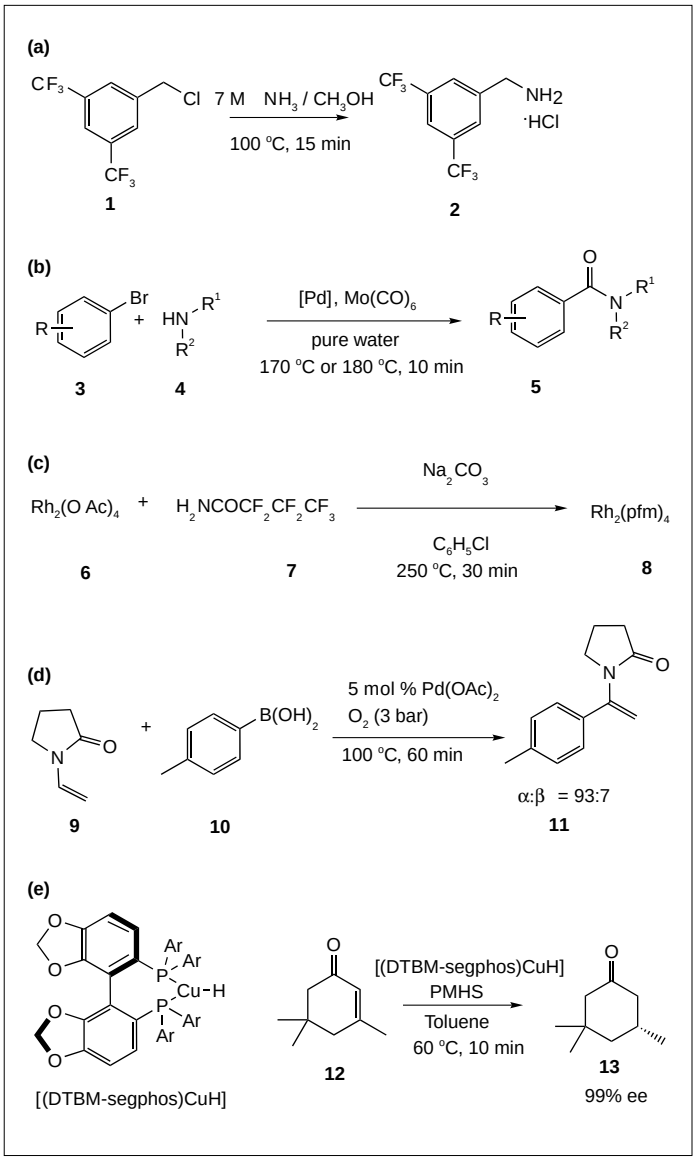

FIGURE 1

Examples of microwave-assisted solution phase syntheses and transition-metal catalyzed reactions.

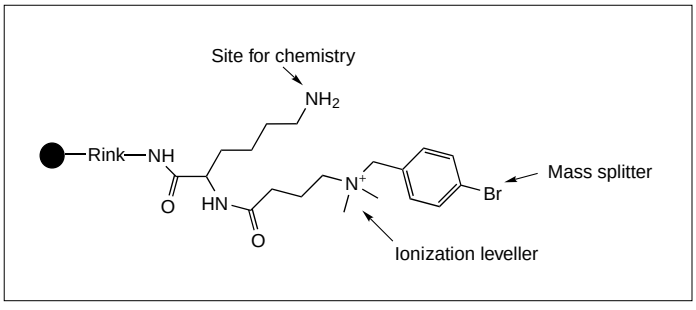

FIGURE 2

Resin-bound analytical construct for reactivity quantification [29].

lack temperature and pressure control and the heating of organic solvents in open vessels often led to violent explosions induced by sparking or electric arcs inside the cavity. The advent of purpose-built commercial microwave reactors (www.biotage.com, www.cem.com; www.milestonesci.com; www.antonpaar.com), incorporating magnetic stirring, temperature and pressure regulation and the ability to process sealed reaction vials in explosion proof cavities, has opened up the entire realm of organic reactions to MAOS. The ability to run high-temperature reactions with volatile substrates and low-boiling solvents has allowed access to reactions that were not previously possible by conventional heating techniques. The use of low-boiling point solvents has the added advantage of simplifying workup. This is exemplified by the atom-economical synthesis of hydrogen halide salts of primary amines by microwave irradiation of halides, mesylates and tosylates in 7 M ammonia (NH_3) in methanol (MeOH) at 130 °C for 0.5–2.5 h (Figure 1a) [9]. This procedure avoids the production of significant amounts of secondary amine side products and requires only evaporation of the solvent to afford products in yields generally greater than 90%, which is ideal for parallel synthesis. The fact that hydrogen halide salts of the primary amine products are obtained directly allows even very volatile primary amines to be accessed in good yields.

The use of water as a solvent in organic reactions is becoming increasingly popular in MAOS. Water, when heated well above its boiling point in sealed vessels, becomes less polar and thus pseudo-organic in nature so that substrates become more soluble [10]. The high heat capacity of water allows for precise control of the reaction temperature. Its lack of flammability makes it safe with pressurized exothermic reactions. Numerous examples of reactions using water as solvent have been reported [11,12]. Most recently aryl bromides **3** were converted to the corresponding secondary and tertiary benzamides **5** in water, using molybdenum hexacarbonyl [$Mo(CO)_6$] [13–16] as the source of carbon monoxide after only 10 min of microwave heating [17] (Figure 1b).

One of the most extensively studied reaction types in MAOS is transition-metal catalyzed reactions. Carbon–carbon and carbon–heteroatom bond-forming reactions, which typically require hours or days to reach completion, often under an inert atmosphere, can be significantly accelerated by employing microwave heating in a sealed vial without the need for an inert atmosphere [18–22].

The catalyst–ligand complex itself can also be synthesized via MAOS. One of the most recent examples is the synthesis of the transition-metal ligand rhodium perfluorobutyramide [$Rh_2(pfm)_4$] **8**, a catalyst used for olefin aziridinations. This is traditionally prepared by refluxing rhodium acetate **6** and perfluorobutyramide **7** in chlorobenzene (C_6H_5Cl) for 60 h under Soxhlet extraction conditions. Using microwave irradiation (Figure 1c), **8** was prepared in substantially less time (30 min) in a sealed vial [23].

MAOS has been widely used in Heck reactions [24,25]. Larhed *et al.* [26] recently reported employing oxygen gas as an efficient re-oxidant of palladium(0) (Pd^0) with good control over the regioselectivity of the oxidative Heck reaction (Figure 1d). The reaction mixture was pre-pressurized with oxygen (~ 3 bar) and heated in a single-mode microwave synthesizer. The reaction time was reduced to 1 h (from 18 h) at 100 °C with 5 mol% palladium loading.

A fast and efficient method for a CuH-based hydrosilylation was recently reported by Lipshutz *et al.* [27]. Exposure of a variety of prochiral substrates to [(*R*)-(–)-DTBM-segphos]CuH [28] (DTBM = 3,5-di-t-butyl-4-methoxy) and polymethylhydrosiloxane (PMHS) under microwave-heated conditions reduces reaction times for these hydrosilylations from hours to minutes without significant erosion in enantiomeric excess (ee) in most cases (Figure 1e).

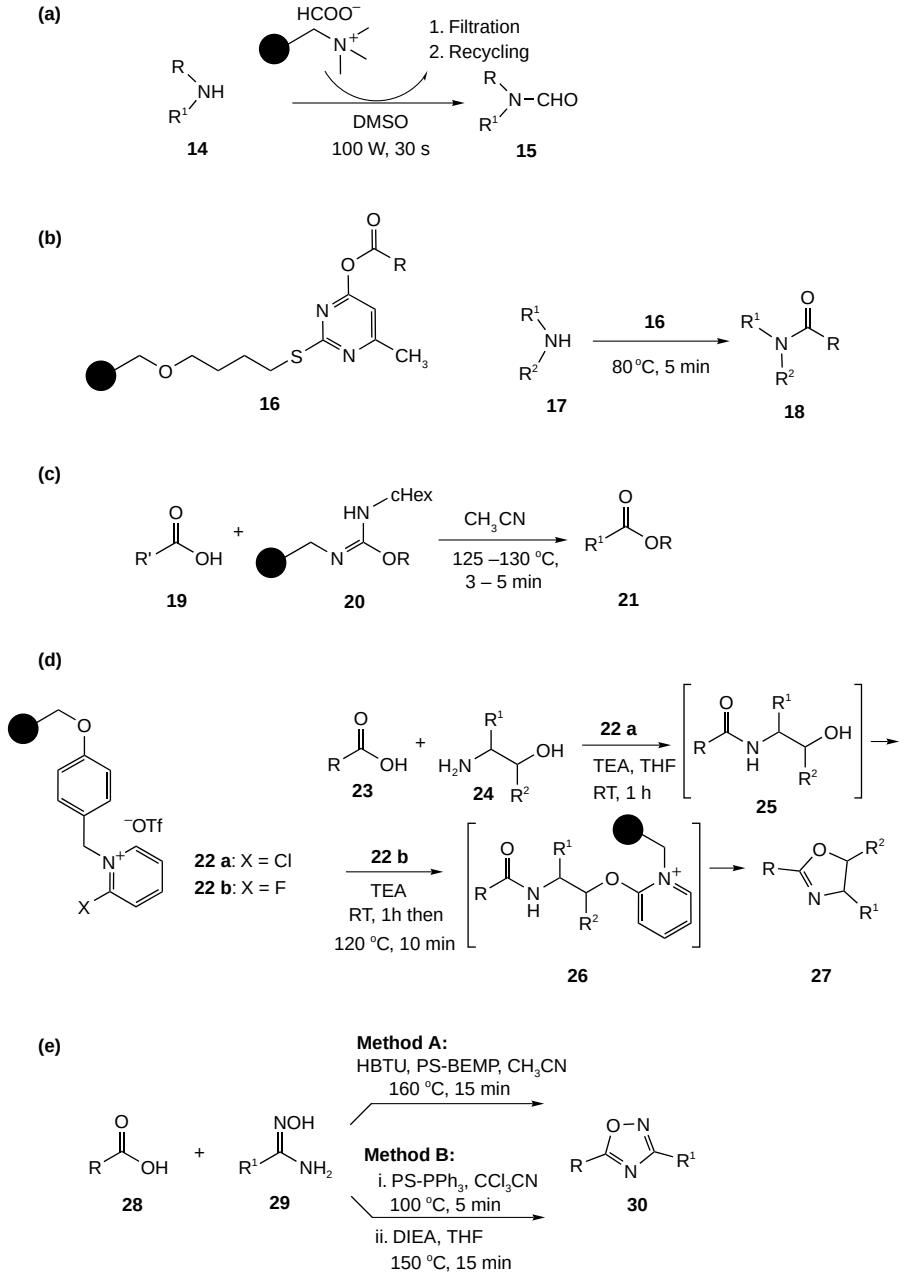

FIGURE 3

Examples of solid-supported reagents in solution-phase microwave synthesis. Abbreviations: TEA, triethylamine; HBTU, *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate; PS-BEMP, 2-t-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine on polystyrene; DIEA, *N,N*-diisopropylethylamine.

Solid-phase synthesis

Microwave heating has been employed to accelerate the reaction rate on insoluble and soluble polymers. Polystyrene, Rink amide, Merrifield and Wang resins are examples of a few resins that have been widely used as insoluble polymers in microwave solid-phase synthesis. MAOS speeds up these conventionally sluggish reactions. The polymer backbones are, in general, stable at the high temperatures used with MAOS for the short periods of time required for most of these reactions. Portal *et al.* [29] have recently utilized a resin-bound analytical construct (Figure 2) to quantify the reactivity of a range of monomers in the Ugi reaction. The effect of variations in concentration on monomer reactivity and product profiles were also rapidly determined using this approach, opening up the way for studying, in a single pot, multiple reactions with a broad range of monomers under identical and self-consistent reaction conditions.

For a comprehensive overview of applications of MAOS in solid-phase synthesis, the reader can refer to reviews [3,30,31] and references therein.

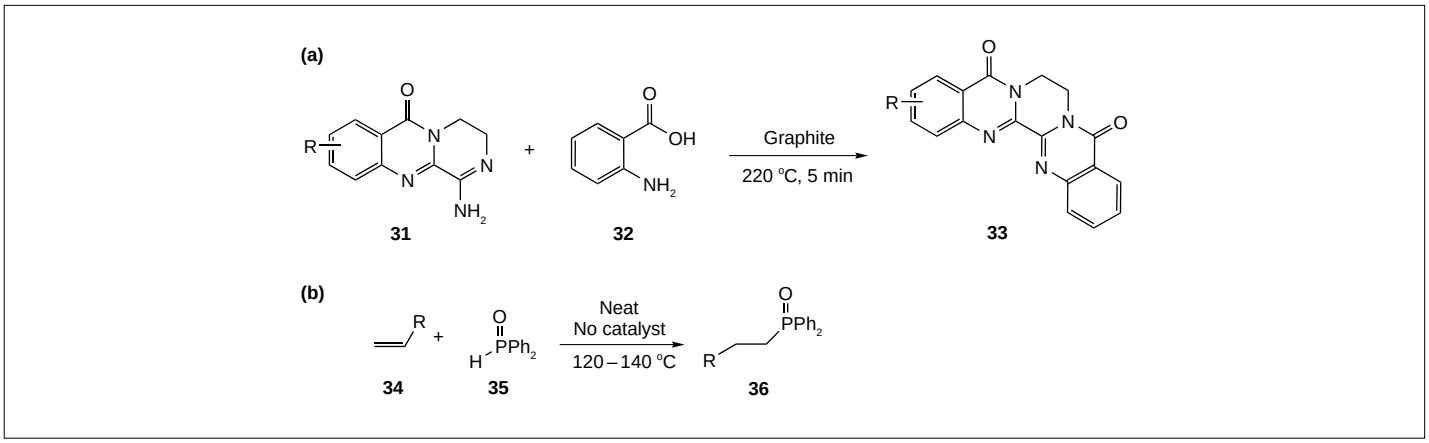

FIGURE 4

Examples of solvent-free microwave reactions.

Solid-supported reagents in solution-phase synthesis

Solid-supported reagents are becoming increasingly popular in solution-phase chemistry, because workup and isolation of products simply involves filtration of the resin and evaporation of the solvent.

Desai *et al.* [32] recently described a rapid and easy route to formamides by microwave-assisted *N*-formylation of primary and secondary amines **14** using an insoluble polymer-supported reagent as a formylating agent (Figure 3a). Microwave irradiation furnished the corresponding formamides in high yields, with reduced reaction time and solvent volume compared with the classical approach.

Several solid-supported acylating [33] and alkylating [34] reagents, such as **16** and **20**, have been reported for selective microwave-assisted acylation of amines **17** (Figure 3b) and esterification of carboxylic acids **19** (Figure 3c) with reaction times as short as 3–5 min.

Crosignani *et al.* [35] recently reported solid-bonded derivatives of Mukaiyama reagent **22a** and **22b**, which they used in the synthesis of a library of 2,4,5-trisubstituted 2-oxazolines **27** (Figure 3d). By giving easy access to 5-substituted 2-oxazolines, this reaction introduced an extra diversity point in 2-oxazoline libraries, which could not be exploited with the methodologies available for solution-phase parallel chemistry. The reaction was complete within 10 min at 120 °C under microwave irradiation, whereas reactions run at room temperature (RT) required 2–3 days to achieve >90% conversion. The workup consisted only in filtration of the resin, followed by evaporation of the solvent.

1,2,4-Oxadiazoles **30** were rapidly synthesized from a variety of readily available carboxylic acids **28** and amidoximes **29** (Figure 3e) [36]. The protocol in method A worked well with a range of amidoximes. 1,2,4-Oxadiazoles **30** could also be generated using method B, through a variety of carboxylic acid chlorides, which were easily obtained *in situ* from diverse carboxylic acids in nearly quantitative yields. The polystyrene bound triphenylphosphine ($PS\text{-}PPh_3$) resin from the first step (method B) did not interfere with the second step and the reaction could be performed in one pot in tetrahydrofuran (THF) without the need for filtration.

Solvent-free synthesis

In the past, MAOS has been carried out under dry or solvent-free conditions, mainly to avoid the hazards of using volatile and flammable organic solvents in domestic microwave ovens. Although the solvent-free technique claims to be environmentally friendly, as it avoids the use of solvents, this is debatable because solvents are often used to pre-absorb the substrates onto, and wash the products off, the solid supports. For neat solids, it is very difficult to obtain a good temperature control at the surface of the solids and local hot spots might be encountered. This can sometimes give rise to unexpected results and inevitably lead to problems regarding reaction predictability, reproducibility and control. For some reactions requiring high temperatures, however, the presence of microwave-absorbing solids can be advantageous. For instance, the best procedure [37] for the preparation of bis-quinazolin-4-ones **33** was found to be via a microwave-assisted Niementowski reaction (Figure 4a), whereby a mixture of the starting amidine **31** and an excess of anthranilic acid **32**, were heated at 220 °C, in the presence of graphite. The sealed vials allowed high temperatures to be reached and prevented sublimation of the anthranilic acid. This reaction, when performed in the presence of solvents, such as *N*-methylpyrrolidinone (NMP) or *N*,*N*-dimethylformamide (DMF), offered only 37% product and a large amount of byproducts.

Neat reactions of liquid substrates can be quite successful. For example, the addition of P(O)–H bonds to alkenes has been accomplished using microwave irradiation in the absence of added solvent or catalyst (Figure 4b) [38]. Tandem hydrophosphinylation reactions with alkynes afforded unsymmetrical species such as phosphine oxide and phosphinates.

Microwave-assisted organic synthesis in drug discovery

Nowadays, MAOS is gaining widespread acceptance in drug discovery laboratories. The rapid acceptance of this technology parallels the rising cost of R&D and decrease in the number of FDA approvals, which have led to what is termed as a productivity crisis [39]. Reducing the cost of failure, either by failing candidates sooner or by improving the overall probability of success, is the most powerful solution to improving R&D productivity. Microwave technology, by accelerating chemical reactions from hours or days to minutes, provides quick results. From time to time microwave heating enables chemistries that were not previously possible by classical methods, expanding the realm of structures accessible to the chemist.

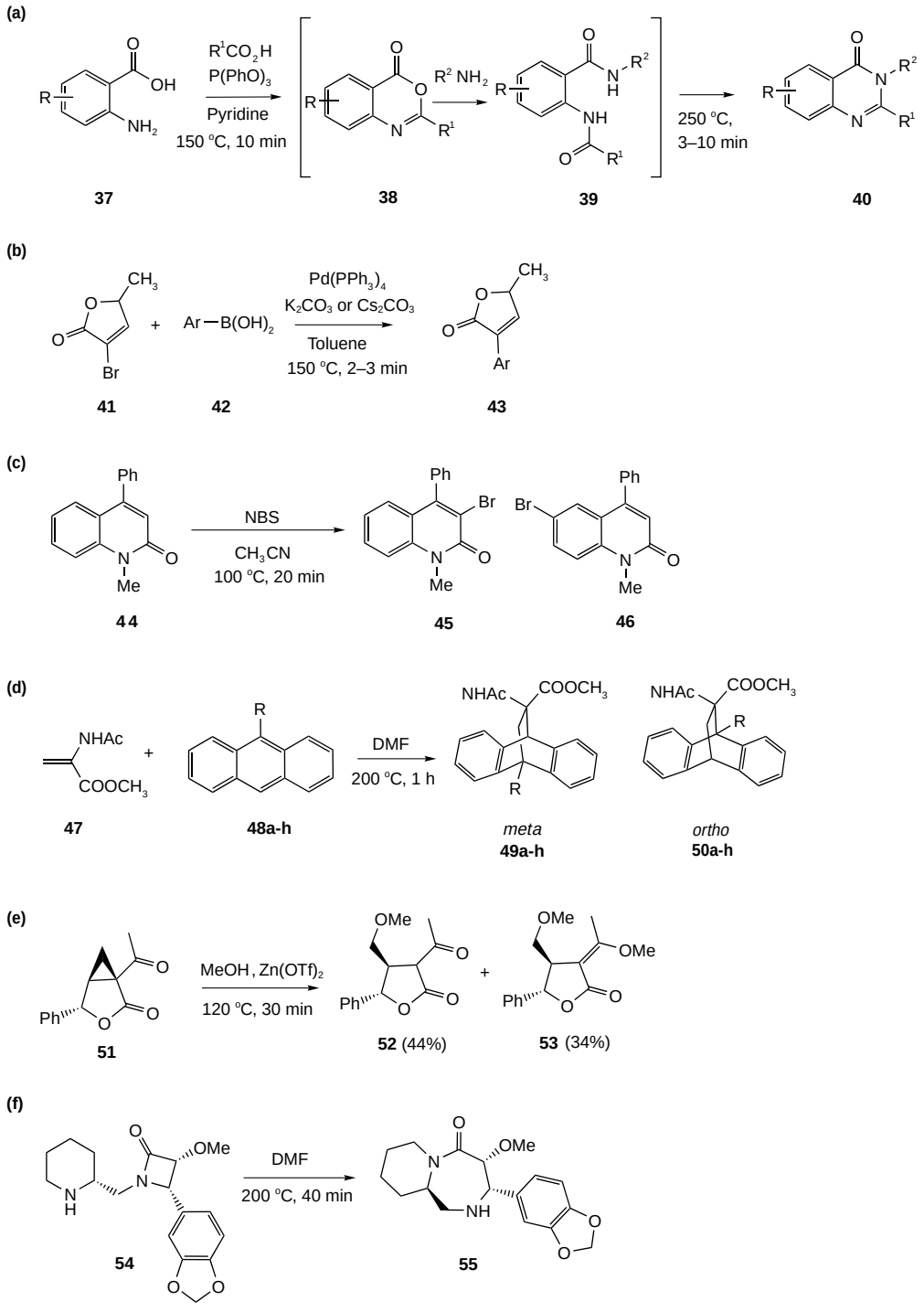

FIGURE 5

Examples of chemo-, regio-, and stereo-selective microwave reactions.

Liu *et al.* [40] have demonstrated the value of MAOS for expanding the accessible chemical space by generating otherwise unavailable reaction products. The one-pot two-step synthesis of 2,3-disubstituted 3*H*-quinazolin-4-ones **40** from anthranilic acids **37** (Figure 5a), has now been adapted to the synthesis of diverse screening libraries and the total synthesis of a number of natural products containing this heterocyclic scaffold.

Effect on chemistry research and development

The short reaction times provided by MAOS make it ideal for rapid reaction scouting and optimization. Most reagents, catalysts and substrates have been shown to survive temperature extremes for short periods of time. Similar to traditional chemistry, the success of reactions is as dependent on factors such as solvent and reagent selection as it is upon temperature and time.

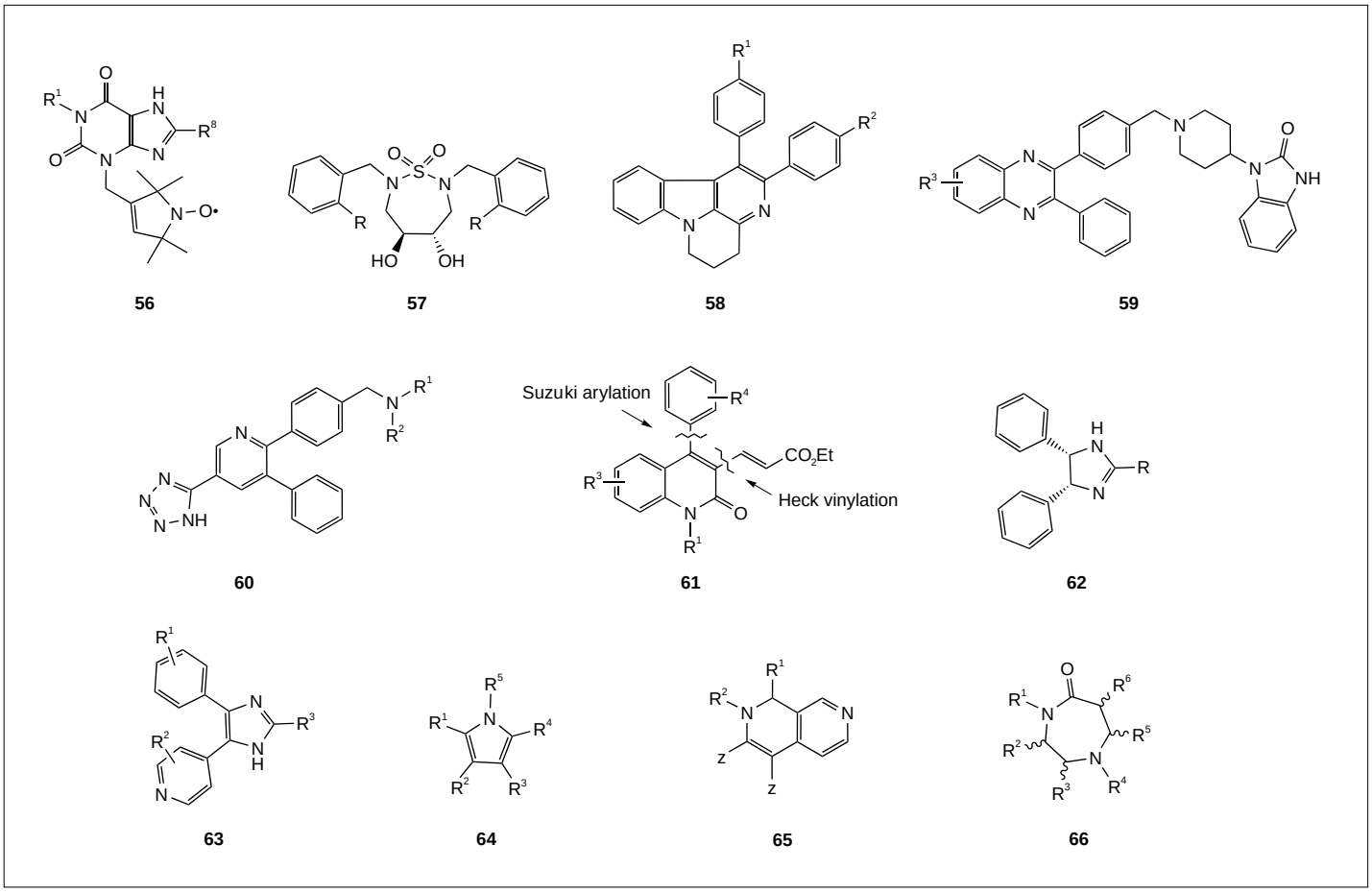

FIGURE 6

Examples of a spin label probe and leads generated by microwave-assisted medicinal chemistry.

For instance the Suzuki-Miyaura coupling of bromofuranone **41** with phenylboronic acid **42** in acetonitrile (CH_3CN) with sodium carbonate resulted in complete decomposition at 90 °C whereas in toluene with potassium carbonate (K_2CO_3), a 40% yield of the coupled product **43** was obtained at 140 °C (Figure 5b) [41].

The efficient use of reaction conditions can be used to obtain the desired chemo-, regio- or stereo-selectivities [42]. For instance, the bromination of quinoline **44** with *N*-bromosuccinimide (NBS) (Figure 5c) [43] was affected by the temperature and the solvent selection. The ease of bromination was crucially dependent on the polarity of the solvent, whereas the reaction regioselectivity was temperature dependent. At 100 °C in CH_3CN there was selective formation of the isomer **46** after 20 min, with only trace amounts of **45**.

The use of appropriate solvents allowed the highly regioselective preparation of a series of conformationally constrained bicyclic bisaryl α-amino acids via microwave-assisted Diels-Alder reactions of 9-substituted anthracenes **48** and 2-acetamidoacrylates **47**, in significantly shorter periods of time (1 h versus 48-72 h; Figure 5d) [44]. With DMF, a polar and highly microwave-absorbing solvent, microwave irradiation at elevated temperatures (200 °C, 1 h) was found to enhance the *meta* regioselectivity and improve reaction yields. Nitrobenzene, which gave good yields of the *meta* product under conventional heating, was not the optimal solvent under microwave irradiation.

The nucleophilic opening of the activated cyclopropane **51** by heating at reflux with zinc triflate [$Zn(OTf)_2$] in MeOH for 24 h was met with little success [45]. Microwave heating allowed investigation of a broader range of conditions so that the cyclopropane **51** could be opened efficiently with methanol at 120 °C after just 30 min to afford the desired product **52** and the corresponding enol ether **53** (Figure 5e).

Microwave synthesizers have also been implemented successfully in a high-throughput workflow utilized to screen different solvent mixtures for the microwave-assisted cationic ring-opening polymerization of 2-nonyl-2-oxazoline [46].

Effect on screening and target discovery

Positron emission tomography (PET) is an imaging technique where pharmaceuticals labeled with short-lived isotopes of mainly carbon and fluorine (^{11}C and ^{18}F with half-lives of 20 and 110 min, respectively) are used for *in vivo* imaging. For successful imaging it is important to have a final product with high specific radioactivity, which makes a short synthetic route crucial. Several microwave-assisted radio-labeling procedures have been reported [47]. Recently, PET ligands with low picomolar affinity at nicotinic acetylcholine receptors (nAChR), which play important roles in various brain functions, were synthesized [48]. Microwave heating was used at multiple stages of the synthesis including the final labeling step. Velikyan *et al.* [49] were able to obtain 0.5–1 nmol

quantities of ^{68}Ga-labeled peptide conjugates (DOTA-D-Phe^1-Tyr^3-octreotide; DOTA=1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) within 10 min with fully retained ^{68}Ga activity. Further purification of the ^{68}Ga-labeled peptide conjugate was not required because the nuclide incorporation was quantitative. Microwave irradiation has also been used to synthesize some spin labeled probes (Figure 6, **56**) for adenosine receptors [50].

Effect on lead generation and optimization

Because of its speed, MAOS is ideally suited for high-throughput chemistry. The first application of microwave-assisted combinatorial synthesis was in the production of libraries of diverse pyridines using a 96-well microtiter plate [51]. Recently, Alcazar [52] compared yields of alkylated products obtained in single-mode and multi-mode instruments. For the multi-mode instrument, he observed the highest yields in the center and lower yields at the corners of the multi-well plate. One of the earliest applications of MAOS in lead optimization was in the synthesis of C2-symmetric HIV-1 protease inhibitors and malarial protease plasmepsin I and II [53]. This has since evolved into cyclic sulfamide analogs (Figure 6, **57**) [54] and nanomolar inhibitors of plasmepsin I and II devoid of cathepsin D inhibitory activity [55].

Lindsley *et al.* [56] described a one-pot microwave-assisted protocol for the synthesis of unnatural canthine alkaloids (Figure 6, **58**) with biological activities beyond those of the natural products. His group also developed two series of potent and selective allosteric Akt kinase inhibitors (Figure 6, **59**) that display an unprecedented level of selectivity for Akt1 and Akt2 [57]. An iterative analog library synthesis approach quickly provided a highly selective Akt1 and Akt2 inhibitor that induced apoptosis in tumor cells and inhibited Akt phosphorylation. In an extension of this work Zhao *et al.* [58] described the synthesis of a novel series of dual Akt1 and Akt2 kinase inhibitors (Figure 6, **60**) using microwave irradiation at various stages.

Glasnov *et al.* [43] synthesized some 4-aryl-3-alkenyl substituted quinolin-2(1*H*)-ones (Figure 6, **61**) as potential maxi-K channel openers, neuroprotectants and antitumor agents, in six steps using microwave synthesis.

Merriman *et al.* [59] reported a new series of imidazolines (Figure 6, **62**) as $P2X_7$ antagonists. The chemistry used to prepare this series included a combined solid- and solution-phase approach that was quite general and amenable to library synthesis. The key step in the synthesis was a microwave cyclization using trimethylsilyl polyphosphate (TMS-PP) to afford the desired imidazoline targets.

2,4,5-Triaryl imidazoles (Figure 6, **63**) were synthesized [60] directly from the keto-oxime in moderate-to-good yields via cyclization to the *N*-hydroxyimidazole and an unprecedented *in situ* thermal reduction of the N–O bond upon microwave irradiation at 200 °C for 20 min.

An efficient one-pot catalytic assembly of pyrroles (Figure 6, **64**) was developed using the Sila-Stetter heterocyclic formation strategy via the thiazolium catalyzed acyl anion conjugate addition of acylsilanes [61]. This approach is multicomponent in nature and can rapidly install substitution at multiple positions of the pyrrole nucleus.

Wipf *et al.* [62,63] developed an expeditious divergent multicomponent reaction (DMCR) method, combining the advantages of microwave reaction acceleration and combinatorial technologies with a libraries-from-libraries concept to prepare 20 allylic

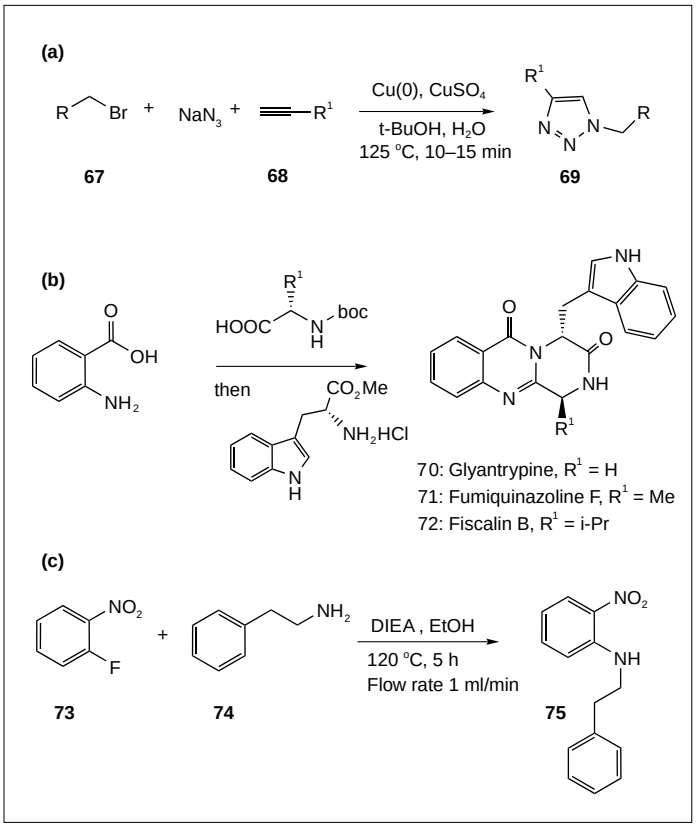

FIGURE 7

Examples of multicomponent and flow-through microwave chemistry.

amides and *C*-cyclopropylalkylamides and create an expanded 100-member library.

1,2-Dihydro[2,7]naphthyridine-4-alkoxycarboxylates (Figure 6, **65**) were prepared in a one-pot synthesis from 3-alkylpyridines and electron-deficient acetylenes mediated by microwave irradiation [64]. The product was obtained from its diene precursor within 20 minutes of microwave irradiation in contrast to 3–5 h required when using conventional heating.

The synthesis of a collection of bicyclic fused diazepinones (Figure 6, **66**) via intramolecular β-lactam ring opening strategy was reported by Vasudevan *et al.* (Figure 5f) [65]. Depending on the chirality of the various inputs (**54**), complete stereocontrol of product **55** formation was achieved. No epimerization was observed in any of the compounds synthesized in this study, at the elevated temperatures used.

A microwave-assisted three-component 'click' reaction was used to prepare a series of 1,4-disubstituted-1,2,3-triazoles **69** from corresponding alkyl halides **67**, sodium azide (NaN_3) and alkynes **68**, in a completely regioselective manner (Figure 7a) [66]. This procedure eliminates the need to handle organic azides, as they are generated *in situ*, making this click reaction more user-friendly and safe. Products are easily isolated by filtration, as the triazole products often crystallize from the reaction mixture.

A microwave-promoted three-component one-pot reaction was developed to provide access to the core pyrazino[2,1-*b*]quinazoline-3,6-dione scaffold, common to several families of alkaloids with significant biological activities (Figure 7b) [67]. By adapting this synthetic strategy, through the use of selected Boc-amino acids and amino acid esters, highly efficient and concise total syntheses

of glyantrypine **70**, fumiquinazoline F **71**, and fiscalin B **72**, were achieved with overall yields of 55, 39, and 20%, respectively.

Effect on process development

Microwave-assisted organic synthesis is beginning to play a greater role in process development, especially in cases where classical methods require prolonged reaction times and forced conditions. Continuous and batch microwave reactors have been constructed for efficient, 'green' synthesis with low-boiling solvents at high temperatures in closed vessels [68]. Commercial microwave systems based on these developments are available.

Batch systems in process development

In a batch process, all the reaction components are combined and held under controlled conditions until the desired process endpoint is reached. When working with large volumes (>1 l), single-mode microwave systems are no longer the obvious choice from a practical point of view and multi-mode cavities might be a better alternative. Microwave processes can produce high temperatures and pressures and any scale-up operation must consider these potential dangers and limitations. All scale-up synthesis should be preceded by bench-scale trials to ascertain safety. Batch reactors have been used in the scale-up of the decongestant and anti-asthmatic drug L-ephedrine [69] and the preservative *n*-butylparaben [70]. A batch reactor was recently used [26] to scale-up the reaction shown in Figure 1d to a multigram scale (10 mmol) using a constant pressure of oxygen and without any special precautions. In this 80 °C, 70 min process, only a minor reduction of the α:β selectivity to 97:3 was encountered.

Flow-through systems in process development

In continuous flow-through systems, reagents are pumped through the microwave cavity, allowing only a portion of the sample to be irradiated at a time. The main drawback is that, for some reactions, not all the components are soluble prior to, or after, microwave irradiation and this can stop the flow as a result of blockage of the tubes. A series of synthetic transformations were successfully and safely scaled up to multigram quantities using focused microwave irradiation with a continuous microwave reactor, developed at Boehringer Ingelheim Pharmaceuticals [71]. The representative reactions that were investigated included aromatic nucleophilic substitution (SNAr), esterification, and the Suzuki cross-coupling reaction. In general, the product yields were equivalent to or greater than reactions run under conventional thermal heating conditions. For the SNAr of 4-fluoro-3-nitroaniline **73** with phenethylamine **74**, the flow-through system provided 54% conversion after 5 h, the total irradiation time per ml of reaction mixture was 24 min (Figure 7c). However, as the reaction progressed, the SNAr product crystallized from the solution as a fine orange powder and the resulting particles eventually clogged the lines and frits, making it necessary to terminate the reaction before complete consumption of the starting material.

Comer and Organ [72] have recently developed a capillary-based flow system for conducting microscale microwave synthesis. Excellent conversions were reported in a variety of metal-free cross-coupling and ring-closing reactions, although reactions that had solids in them did not seem to pose a concern and capillaries coated internally with a thin film of Pd metal were capable of catalyzing reactions. Reagents in separate syringes could also be co-injected into the capillary, mixed and reacted, with none of the laminar flow problems that plague microreactor technology.

Conclusion and future trends

One of the biggest tasks facing the pharmaceutical companies is to accelerate drug development by increasing productivity, discovering new leads and generating novel therapeutic agents against the vast numbers of potential drug targets. The goal of the medicinal chemist is to develop leads efficiently to identify strong candidates early so as to minimize failure rate of compounds in clinical trials and move drugs into the marketing pipeline quickly. Rapid lead generation and optimization has recently been facilitated by the emergence of MAOS and the technique is today one of the major tool for the medicinal chemist, where speed of discovery equals competitive advantage in terms of intellectual property, positioning in the market place and ability to deliver critically needed new chemical entities (NCEs) and candidate drugs.

However, the use of MAOS alone just moves the bottle-neck downstream in the drug development process. An important next step in the future development of medicinal chemistry would be to overcome and avoid down-stream congestion, by streamlining the entire process of synthesis–workup–purification–analysis. Combining MAOS and solid-supported reagents will, hence, gain greater importance and will become a significant technique in speeding up the drug development process, especially because the combination is easy to automate.

Interest in MAOS from the process R&D and production engineers has increased substantially during the last two years. The development of batch, semi-batch and continuous flow systems will continue and with time the availability of more-dedicated systems for large-scale synthesis will help overcome the process chemist's apprehension towards MAOS. A similar reluctance was expressed by medicinal chemists when dedicated systems were introduced into the market, a situation that has rapidly changed, as evident from the burgeoning list of publications and the number of conferences and conference contributions on the subject.

MAOS is undoubtedly going to play a major role in chemistry development; this is substantiated by the fact that in most pharmaceutical and biotechnology companies microwave synthesis is the vanguard methodology today.

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