Chapter 2
Microwave-Assisted Syntheses in Organic Chemistry

Nóra Zs. Kiss, Erika Bálint and György Keglevich

Abstract The second part focuses on the summary of typical organic chemical reactions selected, such as coupling reactions (C–C bond formation reactions, carbon–heteroatom bond formations), condensations (aldol-type-, Claisen-, Knoevenagel reaction), multicomponent reactions (Mannich-, Biginelli-, Hantzsch-, Bucherer–Bergs-, Strecker-, Gewald-, Kabachnik-Fields-, Kindler-, Passerini-, Ugi- and domino reactions), cycloadditions (including Diels–Alder reactions). The authors tried to compile fashionable reactions that have been reviewed less in the past years.

Keywords Microwave · Organic chemical reactions · C–C and C–heteroatom coupling reactions · Condensations · Multicomponent reactions · Cycloadditions

2.1 Introduction

In the last decades the MW technique has been intensively used to carry out organic reactions of almost all kinds, and has become a useful non-conventional means of performing organic syntheses. This chapter is aimed at giving insights into the new trends of MW-assisted chemistry, placing the stress on the substantial areas of up-to-date synthetic organic chemistry by presenting a selection of the recent literature.

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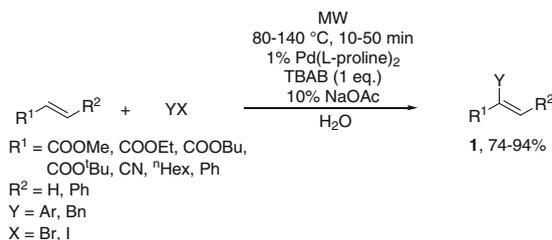
2.2 Coupling Reactions

Carbon-carbon bond forming reactions represent a hot topic in organic chemistry that may benefit from the advantages of MW irradiation resulting in shorter reaction times, as well as simplified accomplishments [1].

Attention has been devoted to develop simple reaction conditions making possible easy product isolations by environmentally benign accomplishments using simple catalysts and green solvents. To face the problems of air sensibility and high cost of typically used *P*-ligands, as well as the difficulties in respect of handling of the reaction mixtures, efforts have been made to develop ligand-free procedures. Driven by environmental concerns, attempts have been made to use water as the solvent.

2.2.1 C–C Bond Formation Reactions

2.2.1.1 Heck Reaction

Singh described a versatile phosphine-free protocol for the arylation and benzylation of alkenes under MW irradiation in water (Scheme 2.1) [2]. The Heck reaction was carried out in the presence of Pd(L–proline)$_2$, an air-stable, water-soluble catalyst complex. The substituted olefins (**1**) were obtained in good yields.

$$R^1 \diagdown R^2 \ + \ YX \xrightarrow[\substack{H_2O}]{\substack{MW \\ 80\text{-}140\ ^\circ C,\ 10\text{-}50\ min \\ 1\%\ Pd(L\text{-}proline)_2 \\ TBAB\ (1\ eq.) \\ 10\%\ NaOAc}} R^1 \diagdown^{\displaystyle Y} R^2$$

R^1 = COOMe, COOEt, COOBu, COO^{t}Bu, CN, ^{n}Hex, Ph
R^2 = H, Ph
Y = Ar, Bn
X = Br, I

**1**, 74-94%

Scheme 2.1 A phosphine-free Heck reaction

Hervé and Len reported the first MW-assisted, ligand-free cross-coupling reaction of unprotected nucleosides in water. The reaction of 5-iodo-2'-deoxyuridine (**2**) with various acrylate derivatives was carried out in the presence of Pd(OAc)$_2$ (Scheme 2.2) [3, 4].
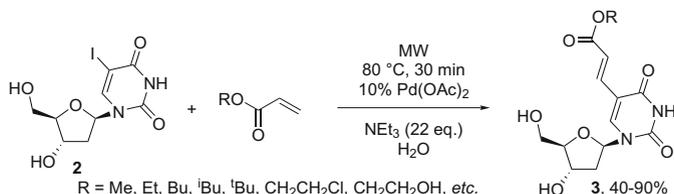
Scheme 2.2 Ligand-free coupling of a nucleoside in water

The use of task-specific ionic liquids (ILs) is also a "hot topic". A MW-assisted ligand-free and base-free Heck reaction was carried out in a task-specific imidazolium ionic liquid by Dighe and Degani (Scheme 2.3) [5]. The in situ formed palladium complex proved to be an excellent catalyst in terms of activity, selectivity and recyclability under MW irradiation.

Scheme 2.3 A ligand- and base-free Heck reaction in ionic liquid
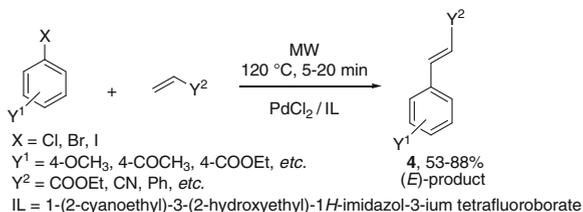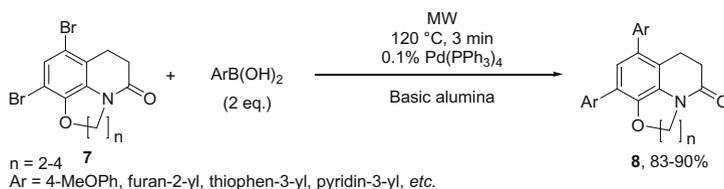

2.2.1.2 Suzuki–Miyaura Reaction

A few examples of Suzuki–Miyaura cross-coupling reactions using water as the solvent carried out under MW irradiation can be found in the literature [6–8]. In this series, an up-to-date environmentally friendly synthesis was reported by Cohen and co-workers for the preparation of various 5–substituted thiazoles in the presence of TBAB as a phase transfer catalyst (Scheme 2.4) [9].

Scheme 2.4 Preparation of 5–substituted thiazoles in water by Suzuki–Miyaura coupling
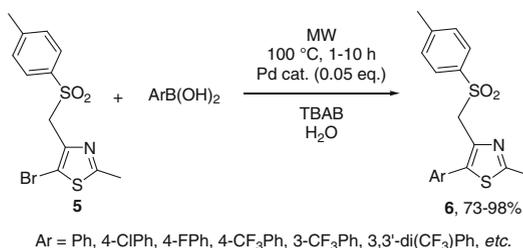
An efficient and solvent-free Suzuki–Miyaura coupling has been developed to form fused tricyclic quinolones using basic alumina as a solid-support and a Pd catalyst under MW irradiation (Scheme 2.5) [10]. The recyclable catalytic system along with the solvent- and base-free conditions, short reaction time and easy handling are remarkable advantages of the synthesis.


n = 2-4 **7**
Ar = 4-MeOPh, furan-2-yl, thiophen-3-yl, pyridin-3-yl, *etc.*

8, 83-90%

Scheme 2.5 A solvent-free Suzuki–Miyaura coupling

Other examples can also be found, where MW irradiation proved to be beneficial in Suzuki–Miyaura cross-couplings by shortening the reaction times (usually to minutes), and increasing the yields, as compared to those obtained by traditional heating [8, 11–13].

2.2.1.3 Hiyama Reaction

A green strategy for the synthesis of biaryls involves a sodium hydroxide activated ligand- and solvent-free Hiyama cross-coupling reaction in the presence of resin-supported Pd nanoparticles under MW heating (Scheme 2.6). A macroporous commercial resin, Amberlite XAD-4, impregnated with Pd nanoparticles (PdNPs) of size 5–10 nm was used efficiently in the coupling of a variety of bromo- and chloroarenes with phenyl-trimethoxysilane. The method of Shah and Kaur benefits from operational simplicity, general applicability and recyclability. The absence of organic solvents, activators and ligands fulfils the requirements of green chemistry [14].

X = Cl, Br
R = 2-Me, 3-Me, 3-COMe, 4-MeO, 4-CHO, 4-COMe, 4-NO$_2$, 4-NHCOMe, *etc.*

9, 76-96%
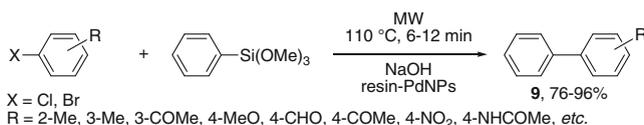
Scheme 2.6 Ligand- and solvent-free Hiyama cross-coupling to form biaryls

2.2.2 Carbon–Heteroatom Bond Formations

Carbon–heteroatom bond formations were also studied intensively under MW-assisted conditions to reduce reaction times, simplify catalyst systems, or eliminate organic solvents.
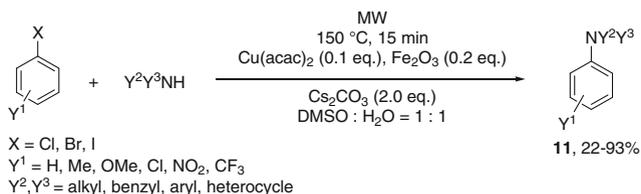
2.2.2.1 Microwave-Assisted C–N Bond Formation

Gupta and Singh described a simple and environmentally-friendly C–N coupling of a wide range of aryl halides and amines under ligand-free and solvent-free MW conditions (Scheme 2.7) [15]. Not only short reaction times were required, but the heterogeneous catalyst applied could be recovered by simple filtration, and could be re-used.

MW
110-160 °C, 20 min

10% NiCl$_2$·H$_2$O
Et$_3$N (1.4 eq.)

X = Cl, Br, I
Y^1, Y^2 = H, 4-Me, 2-NH$_2$, 4-CF$_3$, 2,4-di-NO$_2$
Y^3, Y^4 = H, alkyl, aryl, benzyl

10, 28-92%

Scheme 2.7 Ligand- and solvent-free C–N coupling of aryl halides and amines

Aryl halides and amines were also subjected to iron/copper co-catalyzed ligand-free reactions under MW irradiation (Scheme 2.8) [16]. It is worth mentioning that the simple reaction conditions were associated with a broad substrate scope.

MW
150 °C, 15 min
Cu(acac)$_2$ (0.1 eq.), Fe$_2$O$_3$ (0.2 eq.)

Cs$_2$CO$_3$ (2.0 eq.)
DMSO : H$_2$O = 1 : 1

X = Cl, Br, I
Y^1 = H, Me, OMe, Cl, NO$_2$, CF$_3$
Y^2,Y^3 = alkyl, benzyl, aryl, heterocycle

11, 22-93%

Scheme 2.8 Iron/copper co-catalyzed ligand-free C–N bond formation

Halopyridines and various nitrogen nucleophiles were subjected to a MW-assisted copper-catalyzed cross-coupling without the use of any ligands or solvents (Scheme 2.9) [17].
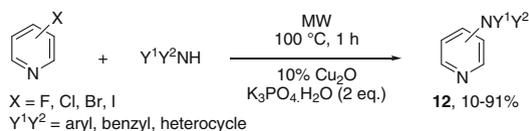
Scheme 2.9 Ligand- and solvent-free C–N bond formation of pyridine-derivatives

N-arylimidazoles of pharmaceutical interest were also prepared by a MW-assisted solvent-free *N*-arylation [18].

2.2.2.2 Microwave-Assisted C–P Bond Formation

The Hirao reaction [19] is an important tool for the formation of P–C bond. See also Sect. 3.5. Many publications highlight the beneficial effect of MW irradiation in the Hirao reaction [20–23]. Keglevich and Jablonkai developed the first *P*-ligand- and solvent-free Pd-calayzed coupling of different >P(O)H species with aryl-bromides in the presence of Pd(OAc)₂ under MW conditions (Scheme 2.10) [24]. This accomplishment is the first example for *P*-ligand-free Hirao reactions.

Scheme 2.10 A novel *P*-ligand-free Hirao reaction
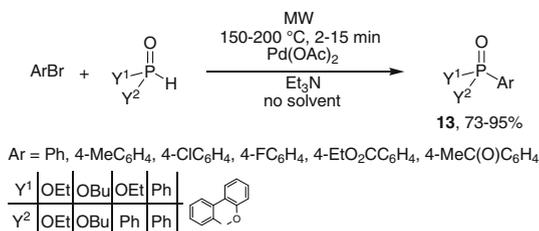
Arylphosphonates, phosphinates or phosphine oxides could all be formed in the coupling reaction of >P(O)H species and aryl halides in the presence of Cu or Ni salts [25]. Starting from the salts of the >P(O)H species, there was no need for any catalysts [26].

2.3 Condensations and Multicomponent Reactions

During condensations, two or more molecules are combined, usually in the presence of a catalyst to form the product with the elimination of water or another simple molecule.

Multicomponent reactions are convergent reactions, in which three or more compounds react to form a product, where the majority of the atoms of the components is incorporated in the newly formed product. Most of the classical

multicomponent reactions involve the participation of carbonyl compounds and/or their derivatives.

In general, traditional conductive heating methods are used to realize condensations and multicomponent reactions. These methods are often slow, and the conventional heating is not really suitable from the point of view of energy efficiency. The use of MW irradiation is more efficient and ecofriendly to carry out these reactions, as shorter reaction times, enhanced reaction rates, and higher yields can be attained in comparison with conventional heating [27].

In this subchapter, several MW-assisted condensations, as well as multicomponent reactions, such as aldol-, Claisen- and Knoevenagel condensations, Mannich-, Biginelli-, Bucherer-Bergs-, Strecker-, Gewald-, Hantzsch-, Kabachnik-Fields-, Kindler-, Passerini-, Ugi- and domino reactions will be discussed.

2.3.1 Aldol-Type Condensations

Aldol condensation is a typical way to form a carbon–carbon bond. In the condensation, an enolizable aldehyde or ketone reacts with a carbonyl compound to form a β–hydroxyaldehyde or β-hydroxyketone, followed by a dehydration step to give a conjugated enone.

A MW-assisted method was developed by Marijani et al. for the synthesis of hydroxy-cyclopentenones (**14**) by the condensation of benzil with ketones carried out in the presence of KOH/EtOH at 180 °C for 2–8 min (Scheme 2.11) [28].
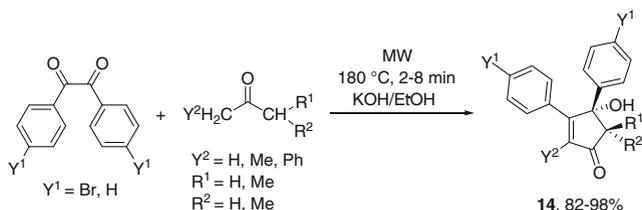
Scheme 2.11 MW-assisted synthesis of hydroxy-cyclopentenones

The MW-assisted aldol-type condensations of 3-methyl-2-cyclohexenones and aromatic aldehydes were studied using $BiCl_3$ as the catalyst in the absence of any solvent (Scheme 2.12) [29].
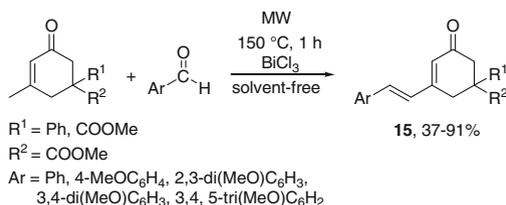

Scheme 2.12 Condensation of 3-methyl-2-cyclohexenones and aromatic aldehydes

2.3.2 Claisen Condensations

The Claisen condensation [30] is the "ester analogue" of the aldol condensation. During the reaction, two esters, or one ester and another carbonyl compound react with each other in the presence of a strong base to form a β-keto ester or a β-diketone.

An ultraviolet absorbent, 4-*tert*-butyl-4′-methoxydibenzoylmethane (trade name Avobenzone) (**16**) was synthesized by the Claisen condensation of 4-methoxyacetophenone and methyl 4-*tert*-butylbenzoate in a household MW oven using sodium amide as the base, and toluene as the solvent (Scheme 2.13) [31].
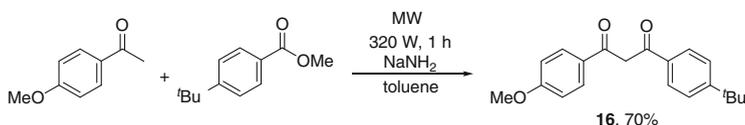

Scheme 2.13 Claisen condensation of 4-methoxyacetophenone and methyl 4-*tert*-butylbenzoate

2.3.3 Knoevenagel Condensations

The Knoevenagel reaction [32] is a modified aldol condensation between an aldehyde or ketone, and an active methylene group containing compound in the presence of a base catalyst. The reaction is usually followed by a spontaneous dehydration step resulting in an unsaturated product.

A high nitrogen containing mesoporous carbon nitride (MCN) was applied as a metal-free base catalyst in the Knoevenagel condensation of aromatic aldehydes with ethyl cyanoacetate (Scheme 2.14) [33]. The reactions were performed in toluene under MW irradiation, and the products (**17**) were obtained in yields of 75–95 %.
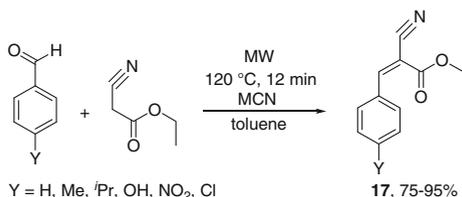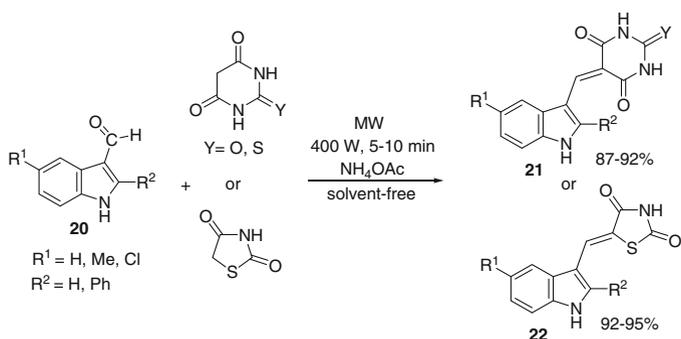

Scheme 2.14 Knoevenagel condensation of aromatic aldehydes with ethyl cyanoacetate

The condensation of 3-α-carboxy ethylrhodanine (**18**) with substituted aromatic aldehydes in the presence of sodium acetate in glacial acetic acid was studied under MW irradiation at 150 °C for 10–15 min (Scheme 2.15) [34]. The reactions afforded 5–benzylidene-3-α-carboxy ethylrhodanine derivatives (**19**) in high yields.

Scheme 2.15 Condensation of 3-α-carboxy ethylrhodanine with aromatic aldehydes

The MW-assisted Knoevenagel reactions of 2,5-disubstituted indole-3-carboxaldehydes (**20**) and active methylene group containing compounds were studied by Biradar and Sasidhar (Scheme 2.16) [35]. The reactions were carried out in a household MW oven, in the presence of ammonium acetate under solvent-free conditions. It was found that without catalyst, the yields were very low and sometimes no reaction occurred.


Scheme 2.16 Knoevenagel reaction of 2,5-disubstituted indole-3-carboxaldehydes
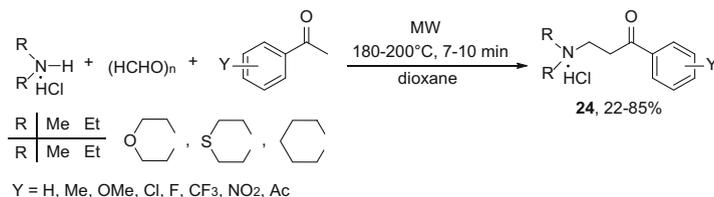
2.3.4 Mannich Reactions

The Mannich reaction [36] is a three-component condensation, where a primary or secondary amine (or ammonia) reacts with an aldehyde and a ketone. The final product is a β-amino-carbonyl compound, also known as a Mannich base.

β-Amino-carbonyl derivatives (**23**) were synthesized in the three-component condensation of aniline derivatives, aromatic aldehydes and cyclohexanone using CeCl₃ as the catalyst under solvent-free and MW conditions (Scheme 2.17) [37].
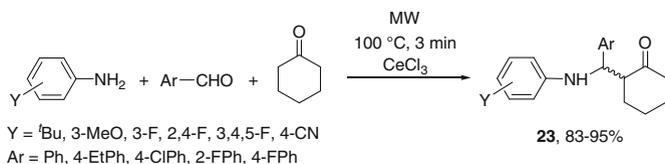
Scheme 2.17 MW-assisted solvent-free condensation of anilines, aromatic aldehydes and cyclohexanone

MW-assisted Mannich reactions of secondary amine hydrochlorides, paraformaldehyde and substituted acetophenones were studied by Luthman and co–workers (Scheme 2.18) [38]. The reactions were carried out in dioxane on a small (2 mmol) and also on a larger (40 mmol) scale.


Scheme 2.18 Mannich reaction of amine hydrochlorides, paraformaldehyde and acetophenones

Mannich-type reactions of secondary amines, aldehydes and acetylene derivatives were investigated by Leadbeater et al. (Scheme 2.19) [39]. The condensations were performed in dioxane, in the presence of CuCl and a small amount of ionic liquid (IL) under MW irradiation. Using IL as the solvent instead of dioxane, a decomposition was observed.
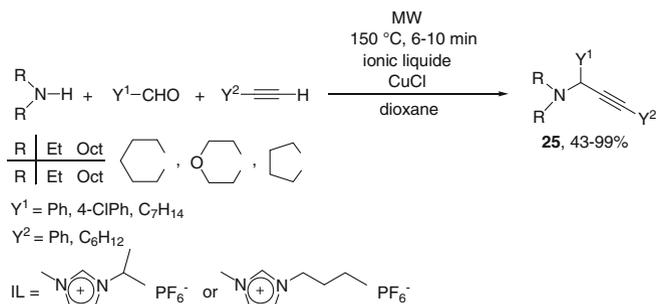
Scheme 2.19 Mannich-type reaction of secondary amines, aldehydes and acetylenes

The MW-assisted condensation of a 2-hydroxy-chalcone (**26**) was studied with secondary amines and paraformaldehyde (Scheme 2.20) [40]. The reactions were performed in dioxane without any catalyst at 100 °C for 10–45 min, and the corresponding products (**27**) were obtained in yields of 81–97 %.


R	Et	Pr	Me	Me	Me
R	Et	Pr	Pr	cHex	Bn
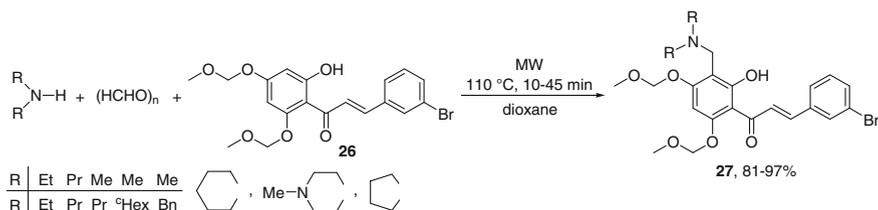
**Scheme 2.20** Condensation of a 2-hydroxy-chalcone

2.3.5 Biginelli Reactions

The Biginelli reaction [41] is a multicomponent one-pot condensation of an aldehyde, a β–keto ester and an urea derivative to afford dihydropyrimidinones, which are of a wide range of pharmaceutical and therapeutic properties [42, 43].

MW-assisted Biginelli reactions of aromatic aldehydes, 1,3-dicarbonyl compounds and urea or thiourea were studied by Japanese researchers (Scheme 2.21) [44]. The condensations were carried out using tributyl borate as the catalyst under solvent-free conditions, and the corresponding dihydropyrimidinones (**28**) were obtained in high yields.


Ar = Ph, 4-MeOPh, 2-ClPh, 3-NO$_2$Ph
R = Me, OMe, OEt
Y = O, S

28, 77-95%
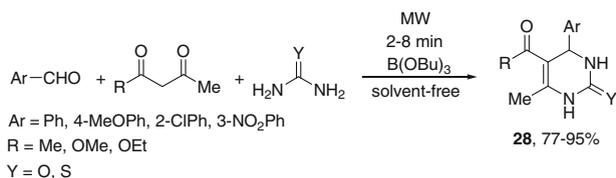
Scheme 2.21 Biginelli reaction of aromatic aldehydes, 1,3-dicarbonyl compounds and ureas

Chinese researchers elaborated a fast and solvent-free MW-assisted method for the synthesis of dihydropyrimidinone derivatives (**29**), but in this case, a heteropolyanion-based IL was applied as the catalyst (Scheme 2.22) [45].
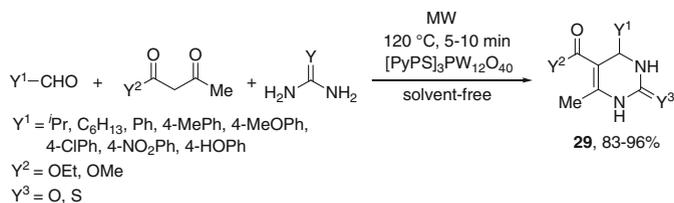
Scheme 2.22 MW-assisted synthesis of dihydropyrimidinones

There is a good example, where the multicomponent reaction of aromatic aldehydes, acetoacetamine derivatives and ureas was performed under solvent- and catalyst-free conditions (Scheme 2.23) [46]. MW irradiation at 120 °C for 12–16 min furnished the dihydropyrimidinones (**30**) in 70–75 % yields.
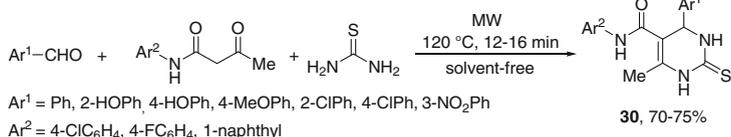

Scheme 2.23 A solvent- and catalyst-free Biginelli reaction under MW irradiation

Fang and Lam reported a modified MW-assisted Biginelli reaction of aromatic aldehydes, 2–oxosuccinic acid and substituted ureas, which led to aryl-oxo-tetrahydropyrimidinyl-carboxylic acid derivatives (**31**) by cyclization accompanied by decarboxylation (Scheme 2.24) [47]. The reactions were performed in THF, and were catalyzed by trifluoroacetic acid (TFA).
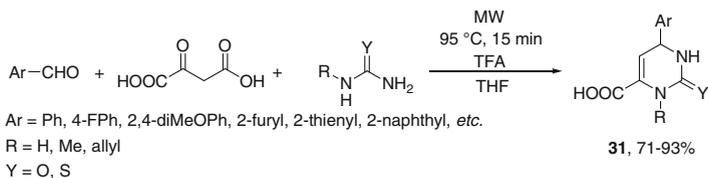
Scheme 2.24 Condensation of aromatic aldehydes, 2–oxosuccinic acid and substituted ureas

The synthesis of 3,4-dihydropyrimidin-2(1H)-ones (**33**) was studied starting from an IL supported aldehyde (**32**), a β–ketoester and an urea (Scheme 2.25) [48]. HCl was used as catalyst, and the reactions were carried out in the absence of solvent under MW irradiation. The corresponding products (**33**) were obtained in good yields after the cleavage of the IL moiety realized by transesterification with NaOMe/MeOH at reflux.
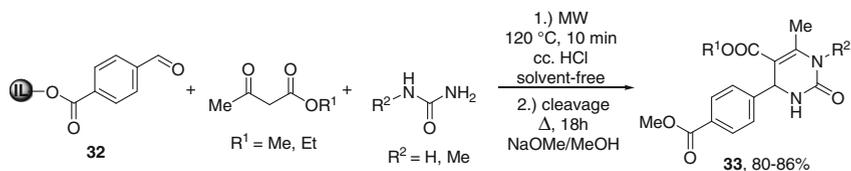
Scheme 2.25 Biginelli reaction of IL supported aldehyde, β–ketoesters and ureas

2.3.6 Hantzsch Reactions

The Hantzsch dihydropyridine synthesis [49] is a four-component reaction with the participation of an aldehyde, two equivalents of a β-ketoester and a "nitrogen donor", such as ammonium acetate, or ammonia. Subsequent oxidation (or dehydrogenation) may lead to pyridine-3,5-dicarboxylates, which may undergo decarboxylation to yield the corresponding pyridines.

Westman and Öhberg developed a MW-assisted Hantzsch reaction of different aldehydes, β-ketoesters and aqueous ammonium hydroxide (Scheme 2.26) [50]. NH_4OH was used as the reagent, and also as the solvent. After an irradiation at 140–150 °C for 10–15 min, the corresponding dihydropyridines (**34**) were formed in moderate to good yields.
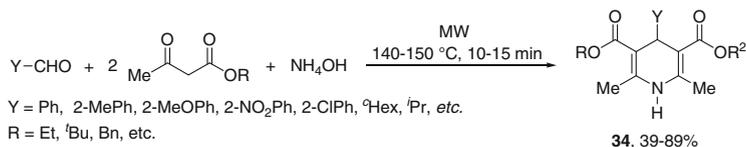
**Scheme 2.26** Hantzsch reaction of aldehydes, β-ketoesters and aqueous ammonium hydroxide

A bismuth nitrate-catalyzed cyclocondensation was reported by American researchers (Scheme 2.27) [51]. A series of dihydropyridines (**35**) were synthesized using a series of aldehydes, 1,3-diketo compounds and ammonium acetate or amines under solvent-free MW conditions.
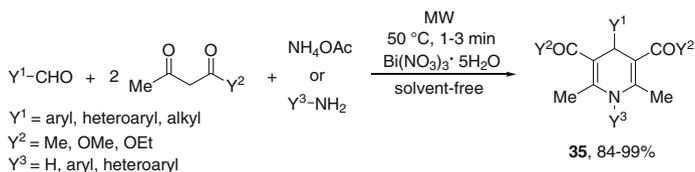

Scheme 2.27 A bismuth nitrate-catalyzed cyclocondensation

Silicotungstic acid nanoparticles dispersed in the micropores of Cr-pillared clay (STA/Cr–P) were used as heterogeneous catalysts for the solvent-free synthesis of 1,4–dihydropyridines (**36** or **37**) (Scheme 2.28) [52]. During these reactions, aryl aldehydes or chalcones were reacted with ethyl acetoacetate and ammonium acetate under continuous MW irradiation at 900 W. After regeneration, the STA/Cr-P catalyst was re-usable for several times.
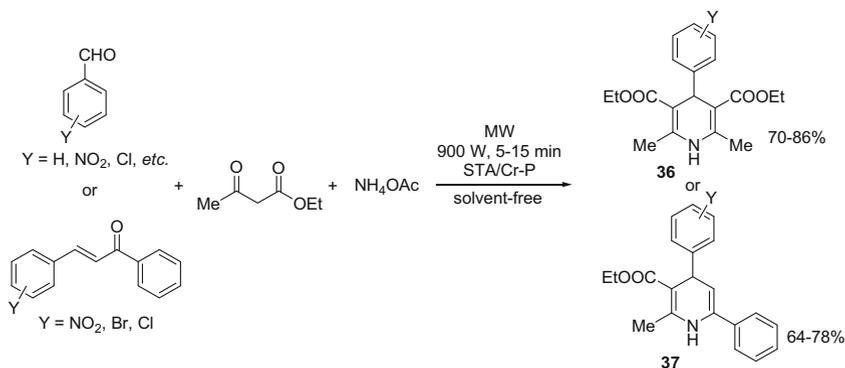
Scheme 2.28 Synthesis of 1,4-dihydropyridines in the presence of STA/Cr-P catalyst

A MW-assisted synthesis of 1,4-dihydropyridines (**38**) using task-specific ILs as a soluble support was described by Bazureau and co-workers (Scheme 2.29) [48]. In the first step, the functionalized IL phase-bound aldehyde (**32**) was reacted with the β–ketoester and aminocrotonate under solvent-free and MW-assisted conditions. 5-*N*-(2-Hydroxyethyl)pyridinium hexafluoroborate ([PEG$_1$py][PF$_6$]) was used as the IL. Then, the IL support was cleaved from the product by transesterification with NaOMe/MeOH at reflux. The desired compounds (**38**) were obtained in yields of 85–86 %.
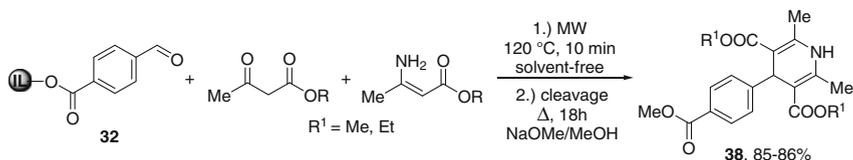

Scheme 2.29 Hantzsch reaction of IL phase-bound aldehyde, β–ketoester and aminocrotonate
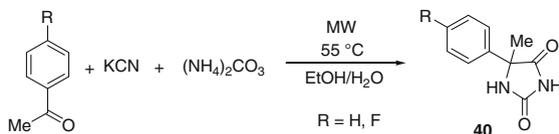
2.3.7 Bucherer-Bergs Reactions

The Bucherer-Bergs reaction [53, 54] is a multi-component transformation with the participation of carbonyl compounds (aldehydes or ketones), cyanohydrines or potassium cyanide and ammonium carbonate, which leads to the formation of hydantoins.

5,5-Disubstituted hydantoins (**39**) were obtained in high yields by the condensation of carbonyl derivatives, potassium cyanide and ammonium carbonate in the presence of EtOH/H$_2$O under MW conditions (Scheme 2.30) [55].

Y^1 = H, ^{i}Bu, ^{c}Hex, Ph, 4-ClPh, 3-MePh
Y^2 = Me, Ph, 4-MePh, 4-MeOPh

39, 83-99%
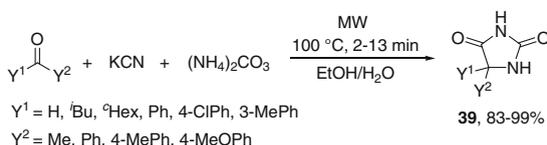
Scheme 2.30 MW-assisted synthesis of 5,5-disubstituted hydantoins

The synthesis of phenylpiperazine hydantoin derivatives was studied by Polish researchers [56]. The compounds were obtained in four steps, where the first step was the Bucherer-Bergs reaction of acetophenone with potassium cyanide and ammonium carbonate under MW conditions (Scheme 2.31).

Scheme 2.31 Bucherer-Bergs reaction of acetophenone, potassium cyanide and ammonium carbonate

2.3.8 Strecker Reactions

The Strecker synthesis [57] provides an amino acid from an aldehyde or ketone. The oxo component is condensed with ammonium chloride in the presence of potassium cyanide to furnish an α-aminonitrile, which is subsequently hydrolyzed to give the desired amino acid.

The Nafion-Fe-catalyzed Strecker reaction of various aldehydes or ketones with amines and trimethylsilyl cyanide were investigated, and the corresponding α-aminonitriles (**41**) were obtained in yields of 49–97 % under solvent-free MW conditions (Scheme 2.32) [58].

Scheme 2.32 A Nafion-Fe-catalyzed Strecker reaction

Y^1	Me	Ph	Ph	3-FPh	4-CNPh
Y^2	Et	H	Et	H	H

Z = Ph, 2-MePh, ⟨⟩ , ⟨⟩ , ⟨O⟩

41, 49-97%
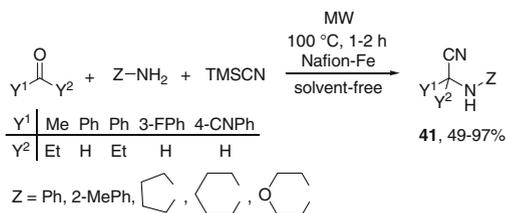
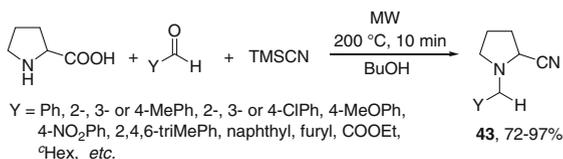A series of α-aminonitriles (**42**) were synthesized via a catalytic Strecker-type reaction of aldehydes, amines and trimethylsilyl cyanide (Scheme 2.33) [59]. The reactions were carried out at low temperature in the presence of Co(II) complex supported on mesoporous SBA-15 under solvent-free MW-assisted conditions.

Scheme 2.33 A catalytic Strecker-type reaction

Ar = Ph, 3-, 4-ClPh, 3-, 4-NO$_2$Ph, naphthyl, *etc.*

42, 80-99%

Y^1	Et			
Y^2	Et	, ⟨⟩ , ⟨O⟩ , *etc.*		
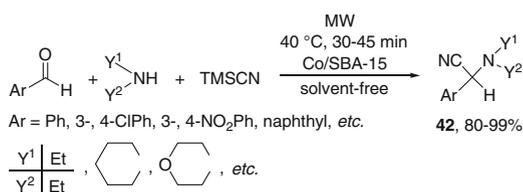
A somewhat Strecker analogous reaction accompanied by decarboxylation was studied by Seidel and co–workers. Proline was reacted with different aldehydes and trimethylsilyl cyanide in butanol under MW irradiation as shown in Scheme 2.34 [60].

Scheme 2.34 A Strecker analogous reaction

Y = Ph, 2-, 3- or 4-MePh, 2-, 3- or 4-ClPh, 4-MeOPh, 4-NO$_2$Ph, 2,4,6-triMePh, naphthyl, furyl, COOEt, ^{c}Hex, *etc.*

43, 72-97%

2.3.9 Gewald Reactions

The Gewald reaction [61] involves the synthesis of 2-aminothiophene derivatives via the multi-component condensation of an α-methylene carbonyl compound, an α-cyanoester and elemental sulfur in the absence of a base.

Kirsh and co-workers developed a MW-assisted procedure for the Gewald reaction of aldehydes, activated nitriles and sulfur (Scheme 2.35) [62]. The condensations were carried out at 70 °C for 20 min using morpholine as the base, and ethanol as the solvent.

Y^1∼CHO + Y^2∼CN + S$_8$ $\xrightarrow[\text{EtOH}]{\substack{\text{MW} \\ \text{70 °C, 20 min} \\ \text{morpholine}}}$

Y^1 = Ph, 3,4-diMeOPh, 4-MeOPh, ^{c}Hex, *etc.*
Y^2 = CN, COOEt, CONH$_2$

44, 50-99%
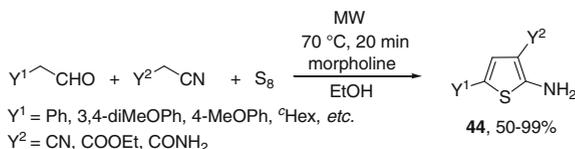
Scheme 2.35 MW-assisted Gewald reaction of aldehydes, activated nitriles and sulfur

The condensation of ketones with cyanoacetate or malononitrile and sulfur was studied under MW conditions (Scheme 2.36) [63]. The multicomponent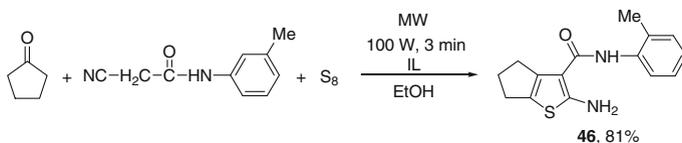 reactions were performed using KF-alumina as the catalyst instead of an organic base, and the 2–aminothiophenes (**45**) were obtained in short times and in yields of 55–92 %.

R^1(C=O)R^2 + Y∼CN + S$_8$ $\xrightarrow[\text{EtOH}]{\substack{\text{MW} \\ \text{100 °C, 3.5-8 min} \\ \text{KF-Alumina}}}$

R^1 = H, Me, Ph
R^2 = H, Me, Et, COOEt   or   (ring)$_n$=O n= 1, 2, 3, 4
Y = COOEt, CN

45, 55-92%
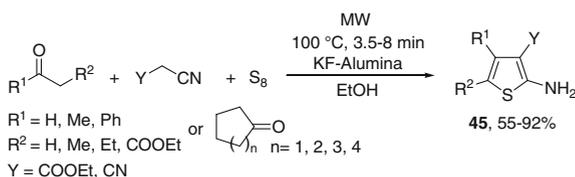
Scheme 2.36 KF-alumina catalyzed Gewald reaction

A guanidine-catalyzed Gewald condensation was reported (Scheme 2.37) [64]. In the course of the reaction, a mixture of cyclopentanone, 2-cyano-*N*-*o*-tolylacetamide and elemental sulfur was irradiated continuously in a MW reactor in the presence of a 1,1,3,3-tetramethylguanidine lactate IL. This reaction was also carried out in ethanol.

(cyclopentanone) + NC−H$_2$C−C(=O)−HN−(tolyl)Me + S$_8$ $\xrightarrow[\text{EtOH}]{\substack{\text{MW} \\ \text{100 W, 3 min} \\ \text{IL}}}$

46, 81%

Scheme 2.37 Condensation of cyclopentanone, 2-cyano-*N*-*o*-tolylacetamide and sulfur

The synthesis of thiophene derivatives (**49**) on a soluble polymer-support utilizing the Gewald reaction was investigated (Scheme 2.38) [65]. The condensations were carried out in a household MW oven starting from various aldehydes or ketones, a PEG-supported cyanoacetic ester (**47**) and sulfur, in the presence of diisopropylethylamine (DIPEA) under solvent-free conditions. Then, the product (**48**) was acylated, and the PEG support was cleaved from the molecule by KCN in methanol. The desired thiophene derivatives (**49**) were obtained in yields of 48–95 %.
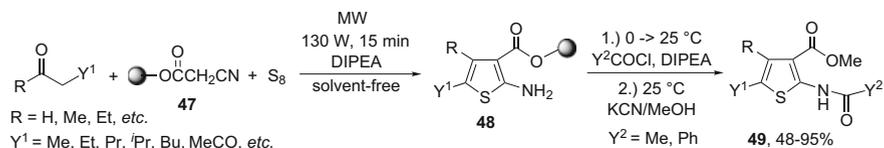
Scheme 2.38 Synthesis of thiophene derivatives on a soluble polymer-support
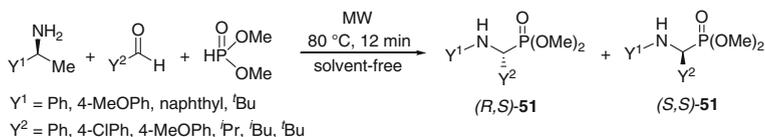
2.3.10 Kabachnik-Fields Reactions

The Kabachnik-Fields reaction [66, 67] is a three-component condensation of an amine, an oxo compound, and a >P(O)H reagent forming α-aminophosphonates or α-aminophosphine oxides, which are synthetic targets of some importance, as the resulting species are the P–analogues of α-amino acids. See also Sect. 3.10.

A MW-assisted catalyst-free and solvent-free Kabachnik-Fields reaction of amines, aldehydes and dimethyl phosphite was described by Chinese researchers (Scheme 2.39) [68]. The condensations were carried out in a multimode MW reactor at 80 °C for 2 min, and the corresponding α-aminophosphonates (**50**) were obtained in yields of 40–98 %.
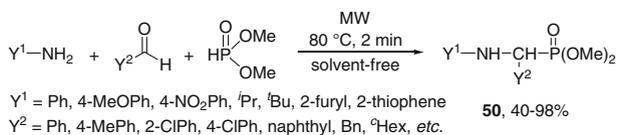
Scheme 2.39 MW-assisted catalyst- and solvent-free Kabachnik-Fields reaction

Ordóñez and co-workers reported a MW-assisted highly diastereoselective synthesis of α–aminophosphonates (**51**) by the three-component reactions of chiral amines, alkyl or aryl aldehydes and dimethyl phosphite (Scheme 2.40) [69]. The condensations were performed in the absence of any catalyst and solvent.


Scheme 2.40 MW-assisted diastereoselective synthesis of α–aminophosphonates

Bis(α-aminophosphonate) pesticides were synthesized by the Kabachnik-Fields reaction of terephthalaldehyde, 2 equivalents of aniline derivatives and diethyl- or dibutyl phosphite under catalyst- and solvent-free MW-assisted conditions (Scheme 2.41) [70].

Scheme 2.41 Synthesis of bis(α-aminophosphonate) pesticides under MW conditions

2.3.11 Kindler Reactions

The Kindler reaction [71] is a three-component condensation of an aldehyde, an amine and elemental sulfur resulting in the formation of thioamides. The modification of this condensation, where ammonium polysulfide is used instead of sulfur, is the Willgerodt-Kindler reaction.

Thiobenzamide derivatives (**53**) were synthesized by the condensation of benzaldehyde or 4-(dimethylamino)benzaldehyde, morpholine and sulfur in a household MW oven (Scheme 2.42) [72]. The reactions were studied using acid and also base catalysts, and it was observed that the bases were more efficient.

Scheme 2.42 MW-assisted synthesis of thiobenzamide derivatives

Another MW-assisted Kindler reaction was reported by Kappe and co-workers (Scheme 2.43) [73]. The three-component condensation of aldehydes, amines and elemental sulfur leading to thioamides **54** was performed using 1–methyl-2-pyrrolidone (NMP) as the solvent at 110–180 °C for 2–20 min.

Scheme 2.43 Kindler reaction of aldehydes, amines and elemental sulfur under MW irradiation

Y^1 = Ph, 3-MePh, 4-MePh, 3-NO$_2$Ph, 4-NO$_2$Ph, Bn, 3-indolyl, pentyl, etc.

| Y^2	H	Pr	^{c}Hex	Bn
Y^3	H	H	H	H

2.3.12 Passerini Reactions

The Passerini reaction [74] is a multi-component transformation among a carboxylic acid, a ketone or an aldehyde, and an isocyanide to form the corresponding α-hydroxy carboxamide.

Brazilian researchers described the solvent-free MW-assited Passerini reaction of substituted carboxylic acids, aldehydes and isonitriles (Scheme 2.44) [75]. The corresponding α-acyloxy carboxamides (**55**) were obtained in good yields at 60 or 120 °C within 1–5 min.
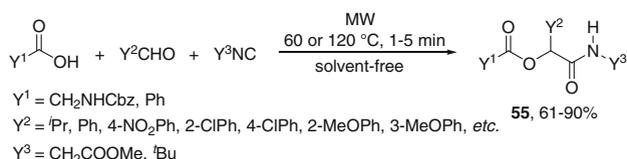

Scheme 2.44 Solvent-free MW-assited Passerini reaction of carboxylic acids, aldehydes and isonitriles

Boron-containing α-acyloxyamide analogues (**57** and **59**) were synthesized from a boron-containing acid (**56**), aldehydes and cyclohexyl isocyanide (Scheme 2.45 (1)), or from a boron-containing aldehyde (**58**), acids and cyclohexyl isocyanide (Scheme 2.45 (2)) in water under MW conditions [76].
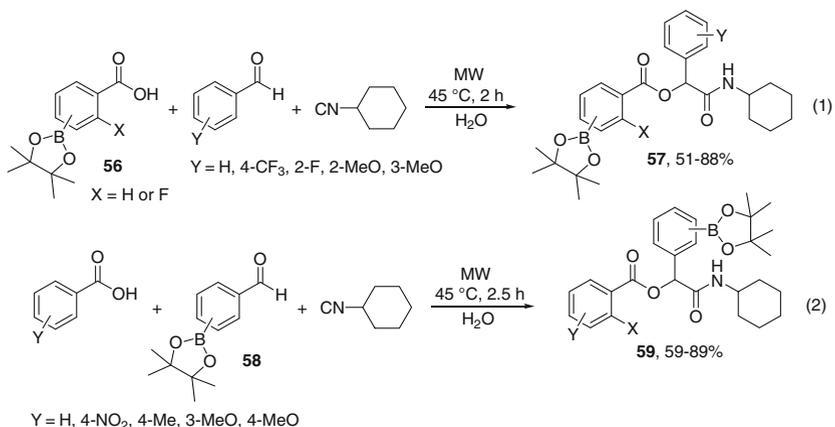
Scheme 2.45 The synthesis of boron-containing α-acyloxyamide analogues

The three-component reaction of trolox derivatives (**60**), furoxan aldehyde (**61**) and phenylethylisocyanide was also described (Scheme 2.46) [77]. The reactions were carried out in water at 60 °C under MW irradiation for 5 min.
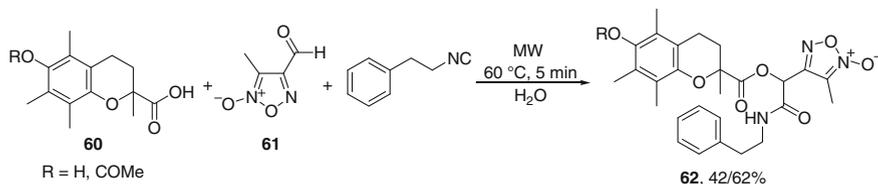

Scheme 2.46 The condensation of trolox derivatives, furoxan aldehyde and phenylethylisocyanide
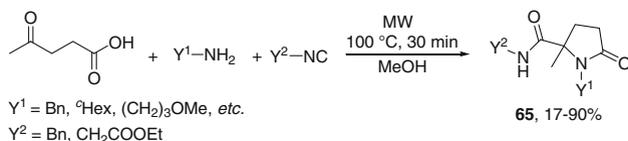
2.3.13 Ugi Reactions

The Ugi four-component condensation [78] with the participation of an amine, an aldehyde or ketone, a carboxylic acid and an isocyanide affords α-aminoacyl amide derivatives, which may be of potential pharmaceutical applications.

A one-pot Ugi reaction followed by intramolecular O–alkylation is an elegant example. The synthesis starts from 2-aminophenols, aldehydes, α–bromocarboxylic acids and isocyanides under MW irradiation (Scheme 2.47) [79].
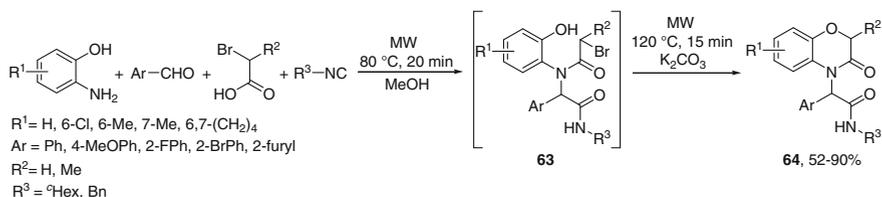

Scheme 2.47 MW-assisted one-pot Ugi reaction followed by an intramolecular O–alkylation

The MW-assisted special Ugi reaction of levulinic acid, amines and isonitriles afforded the corresponding lactams (**65**) in moderate to excellent yields at 100 °C after 30 min (Scheme 2.48) [80].

Scheme 2.48 Ugi reaction of levulinic acid, amines and isonitriles under MW conditions

The synthesis of five- and six-membered lactams via Ugi reaction was also reported (Scheme 2.49) [81]. The condensation of 4-acetylbutyric acid or levulinic acid, amines and isocyanides was carried out under solvent-free MW conditions in a short time.
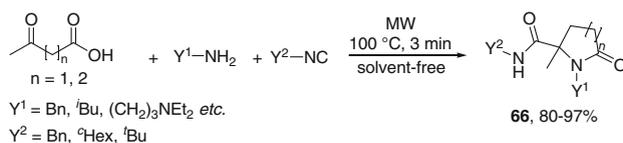

Scheme 2.49 The synthesis of five- and six-membered lactams via MW-assisted Ugi reaction
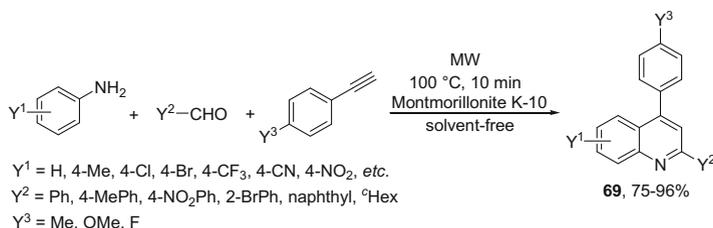
2.3.14 Domino Reactions

In the domino reaction, called also tandem or cascade reaction, two or more transformations take place under the conditions applied without adding any additional reagents or catalysts. These reactions may include multistep synthesis and among others, protection-deprotection steps. Work-up procedures and purifications can be avoided.

Efficient four- and six-component domino reactions were developed, where 2–(2′–azaaryl)imidazoles (**67**) and *anti*-1,2-diarylethylbenzamide derivatives (**68**) were obtained under solvent-free MW-assisted conditions (Scheme 2.50 (1) and (2)) [82].
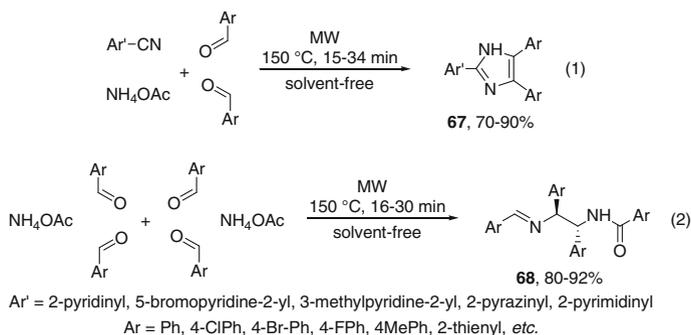
Scheme 2.50 MW-assisted solvent-free four- and six-component domino reactions

Substituted quinolones (**69**) were prepared by a montmorillonite K-10 catalyzed multicomponent domino reaction of amines, aldehydes and terminal arylalkyne under MW irradiation (Scheme 2.51) [83].

Scheme 2.51 Montmorillonite K-10 catalyzed multicomponent domino reactions
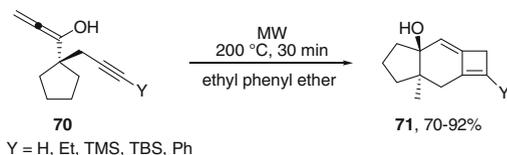
2.4 Cycloadditions

Cycloaddition reactions are pericyclic reactions in which two or more unsaturated compounds are combined with the formation of a cyclic adduct. Thus, cycloadditions provide heterocyclic and multicyclic scaffolds in a single-step. Cycloadditions involving atomic efficient transformations represent another widely investigated group of MW-assisted organic reactions [84].
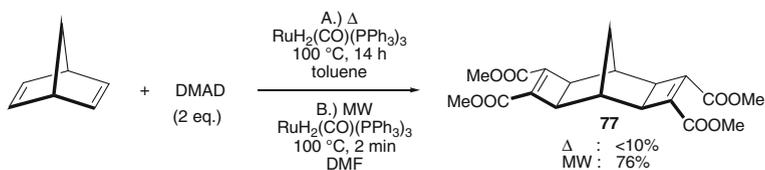
2.4.1 [2+2] Cycloadditions

[2+2] Cycloadditions provide a synthetic tool towards four member rings, such as cyclobutanes, cyclobutenes, β-lactams, oxetenes, cyclobutanones, and their derivatives. These reactions usually require photochemical activation, or the use of a Lewis acid under thermal conditions. A few examples were described, where MW irradiation was found to be beneficial [85].

Ovaska reported a facile MW-assisted intramolecular [2+2] cycloaddition starting from germinal allenyl-propargyl-substituted cyclopentane derivatives (**70**), leading to strained tricyclic 5–6–4 ring systems (**71**) resembling to natural sterpurenes (Scheme 2.52) [86].

Scheme 2.52 The formation of strained tricyclic 5–6–4 ring systems

A similar regioselective intramolecular cycloaddition was described for the formation of bicyclic compounds by Brummond and co-workers. Bicycloalkadienes were formed efficiently when **72** was irradiated by MW at 250 °C in toluene, in the presence of an IL as an additive (Scheme 2.53) [87].

Scheme 2.53 MW-assisted regioselective intramolecular cycloaddition leading to bicycloalkadienes

72

R^1 = Bu, TMS, Ph
R^2 = H, Me

73, 63-74%

An intermolecular Staudinger [2+2] cycloaddition of a phenyl thiodiazoacetate to an imine was enhanced by MW irradiation (Scheme 2.54). The authors aimed at the investigation of nonthermal microwave effects (see also Chap. 4.), and they found no significant difference in the stereoselectivity of the MW-assisted or the thermal variation. However, the reaction speed was somewhat increased under MW conditions [88].

Y = H, Me, OMe, Cl, CF$_3$, NO$_2$

74
cisz / transz
not isolated

Scheme 2.54 A MW-enhanced intermolecular Staudinger cycloaddition

A regiospecific protocol was described for the formation of highly functionalized dienes. 2–Amino-3-dimethylaminopropenoates were reacted with acetylene derivatives to furnish eventually 1–amino-4-(dimethylamino)buta-1,3-diene derivatives (**76**) (Scheme 2.55). The reaction takes place via a cyclobutene intermediate (**75**) by retro-electrocyclisation [89].

Y = COPh, COMe, Cbz
R^1, R^2 = H, COOMe, COOEt, COO^{t}Bu, CF$_3$

75

76, 40-92%

Scheme 2.55 A regiospecific [2+2] cycloaddition leading to buta-1,3-diene derivatives

Pfeffer and co-workers investigated the synthesis of dicyclobutene tetraester **77** by the reaction of norbornadiene and DMAD in the presence of [RuH$_2$(CO)(PPh$_3$)$_3$] as a catalyst complex. While under conventional heating almost no product formation was obtained, under MW irradiation, the corresponding cycloadduct was formed already after 2 min (Scheme 2.56) [90].

Scheme 2.56 MW-assisted synthesis of a dicyclobutene tetraester

2.4.2 [3+2] Cycloadditions

1,3-Dipolar cycloadditions are among the most efficient procedures to form five-membered heterocycles [84]. The reaction of azides with alkynes or nitriles are powerful "click reactions" resulting in 1,2,3-triazoles or tetrazoles. Under traditional thermal conditions, these cycloadditions require often high reaction temperatures.

The copper-catalyzed azide–alkyne cycloaddition (CuAAC) is one of the best "click reactions" to date, as the use of Cu(I) catalysts provides a significant rate acceleration as compared to the uncatalyzed 1,3-dipolar cycloaddition [91]. Several examples confirmed that further enhancement can be obtained by MW irradiation [92].

A new green method have been developed for the formation of 1,2,3-triazoles by Taher and co-workers. A highly active and stable poly-phenylenediamine supported copper(I) catalyst (Cu(I)-pPDA) was found to promote the 1,3-dipolar cycloaddition between terminal alkynes and azides (Scheme 2.57). Thus, the MW-assisted solvent-free accomplishment provides 1,2,3-triazoles (**74**) of pharmaceutical importance with excellent yields [93].

Y^1 = H, Br
Y^2 = Pr, Bu, CH$_2$OH, CH$_2$CH$_2$OH, COOMe, COOEt, Ph, 4-MeOPh, *etc.*
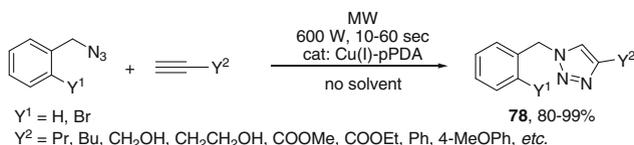
Scheme 2.57 An environmentally benign synthesis of 1,2,3-triazoles

Other metal-catalyzed azide–alkyne cycloaddition reactions have also been reported under MW heating. The synthesis of 1,2,3-triazoles via Ru-catalyzed azide–alkyne cycloaddition (RuAACs) was described by Fokin. It is noteworthy that while the 1,4-disubstituted triazoles were obtained in the Cu(I)-catalyzed azide–alkyne cycloaddition, the Ru-catalyzed version led to the 1,5-regioisomers of 1,2,3-triazoles (Scheme 2.58). MW irradiation provided higher yields, cleaner products in shorter reaction times, as compared to the results obtained on traditional heating, upon which by-products were also formed [94].

Scheme 2.58 MW-assisted Ru-catalyzed azide–alkyne cycloaddition

Y^1 = H, Me, OMe, Cl, I, COOEt
Y^2 = alkyl, heteroaryl

79, 43-92%

An interesting example for 1,3-dipolar cycloadditions is the reaction of an azaphosphonate and an acetylenic ester to furnish the corresponding 1,2,3-triazole as a mixture of two regioisomers (**80A** and **80B**) (Scheme 2.59). While the reaction took place in toluene at 110 °C after 30 h, the solvent-free MW-assisted variation was complete after 5 min [95].

80A   92%   **80B**
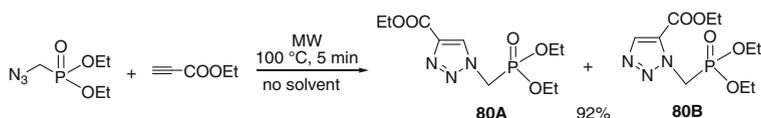
Scheme 2.59 1,3-Dipolar cycloaddition of an azaphosphonate to an acetylenic ester

Kappe described the first example of an organocatalytic tetrazole-formation under MW-assisted conditions. The catalyst (5-azido-1-methyl-3,4-dihydro-2H-pyrrolium azide) was formed in situ. The cycloaddition of azides with organic nitriles resulted in a series of 5-substituted-1H-tetrazoles in high yields (Scheme 2.60) [96].

Y^1 = Ph, 4-MePh, 4-ClPh, 4-CF$_3$Ph, 3-MeOPh, 3-NO$_2$Ph, 2-furyl
Y^2 = H, Na, TMS

81, 79-95%
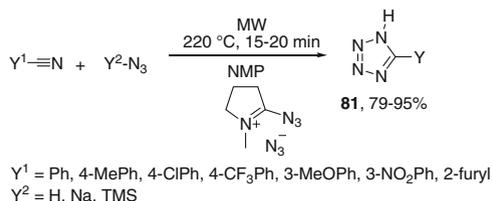
Scheme 2.60 Organocatalytic tetrazole-formation under MW irradiation

2.4.3 Diels–Alder Cycloadditions

The [4+2] cycloaddition of a conjugated diene and a dienophile is widely used to form highly functionalized and fused ring systems. In most cases, the syntheses take place with a high degree of chemo-, regio- and stereoselectivity.

Triazoles are known for their poor reactivity in [4+2] cycloaddition reactions. However, an example was described in which the 1,2,3-triazole ring acted as a diene towards dimethyl acetylenedicarboxylate (DMAD) in MW-assisted

solvent-free Diels–Alder cycloadditions followed by a rearrangement to afford functionalized pyrazole heterocycles (**83**) (Scheme 2.61). The yields could be increased using a supported Lewis acid catalyst, which could be recycled at least five times without a decrease of activation [97].
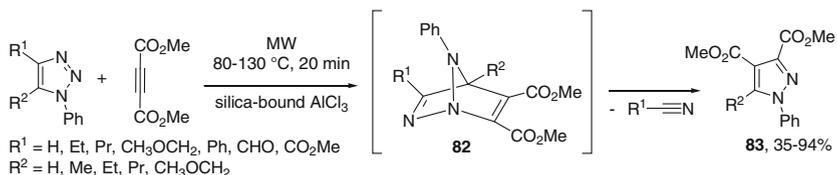
Scheme 2.61 MW-assisted solvent-free [4+2] cycloaddition of triazoles to DMAD

Zheng observed the Diels–Alder reaction between Danishefsky's diene and ethyl α-substituted acrylate derivatives to provide cycloadducts **85** (after deprotection with (+)-10-camphorsulfonic acid (CSA) or pyridinium p-toluene sulfonate (PPTS) from **84**) (Scheme 2.62). The MW heating drastically accelerated the cycloaddition resulting in the desired products in high yields. Compared to the traditional thermal conditions, the method of Zheng offers a 14–48-fold rate acceleration with serious increase in the yields. The adducts so-obtained are useful intermediates in the synthesis of a biotin conjugate of monocyclic cyanoenone with high antiinflammatory activity [98].
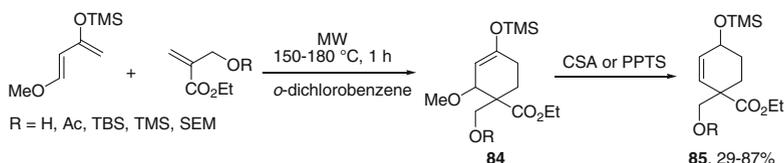
Scheme 2.62 An effective MW-assisted [4+2] cycloaddition of Danishefsky's diene

The MW-assisted intramolecular Diels–Alder cyclization of alkenylaminofuranes at 180 °C in *o*-dichlorobenzene led to 4-monosubstituted indoles (**87**) after dehydrative aromatization of intermediate **86** (Scheme 2.63). Interestingly, no reaction was observed on conventional heating, whereas under MW-assisted conditions, the cyclization furnished the desired 4-substituted indoles in high yields [99]. Thus, the strategy shown is a convenient alternative to the transition metal-mediated coupling processes affording such heterocycles.
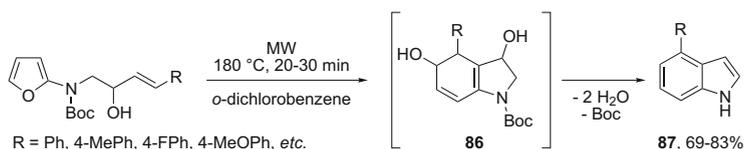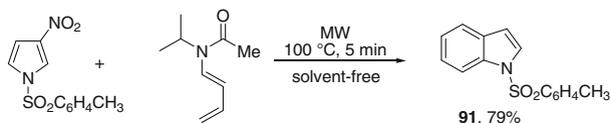
Scheme 2.63 Intramolecular Diels–Alder cyclization of furan derivatives

Kočevar developed an efficient synthesis of 1,5,6-trisubstituted indoles involving two MW-assisted steps. The first step is the Diels–Alder cycloaddition reaction between (Z)-1-methoxybut-1-en-3-yne with 2H-pyran-2-ones (88) yielding substituted aniline derivatives (89). In the next step, the adducts underwent intramolecular cyclization under acidic conditions to give the corresponding indole derivatives (90) (Scheme 2.64). It is worth mentioning that the analogous cycloaddition reactions carried out under high-pressure conventional heating conditions needed very long reaction times up to 138 days, and in two cases anomalous products were obtained [100].

R^1 = Me, CH_2CO_2Et,
R^2 = COMe, COEt, CO_2Me, CO_2Et
R^3 = Me, Ph, Bn
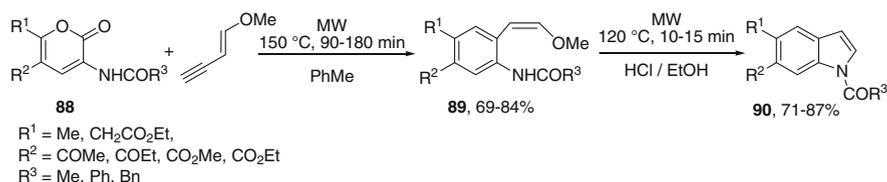
Scheme 2.64 MW-assisted synthesis of 1,5,6-trisubstituted indoles

The Diels–Alder cycloaddition of 3-nitro-1-(p-toluenesulfonyl)pyrrole with N-acetyl-N-isopropyl-1,3-butadiene afforded an indole derivative (91) under solvent-free MW-assisted conditions after the elimination of the nitro group and in situ aromatization [101]. It is noted that the reaction did not occur on conventional heating (Scheme 2.65).

Scheme 2.65 Solvent-free MW-assisted [4+2] cycloaddition of a pyrrole derivative

A MW-assisted intramolecular didehydrogenative Diels–Alder reaction of styrene-ynes (92) was reported to furnish fluorophores 93 (Scheme 2.66) [102, 103].

X = H, Cl
Y = COH, COMe, COPh, CO_2Me, SOPh, SO_2Me, SO_2Ph, $PO(OEt)_2$
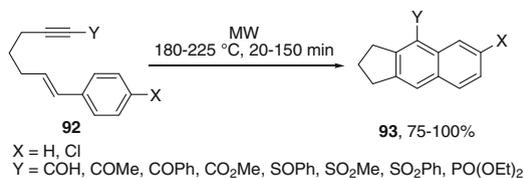
Scheme 2.66 Didehydrogenative Diels–Alder reaction of styrene-ynes under MW conditions

4-Substituted-2,3-dihydrofuro[2,3-b]pyridines and 5-substituted-3,4-dihydro-2H-pyrano[2,3-b]pyridines (**95**) featuring close structural similarity to bioactive molecules were obtained by the intramolecular hetero Diels–Alder cycloaddition of alkyne triazines (**94**) under MW conditions in good yields (Scheme 2.67) [104]. MW activation proved to be efficient to promote the cycloaddition reaction.
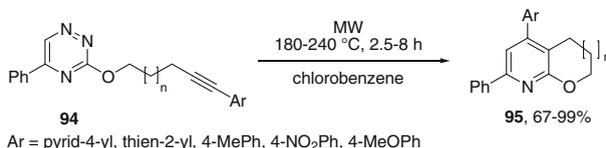

Scheme 2.67 Intramolecular inverse electron demand Diels–Alder reactions under MW irradiation

1,4-Dihydropyridines (**97**) were prepared by an aza-Diels–Alder [4+2] cycloaddition strategy (Scheme 2.68) promoted by MW irradiation. The 1,4-dihydropyridine prepared (**97**) was converted further to antihypertensive drug Amlodipine (not shown here) [105].
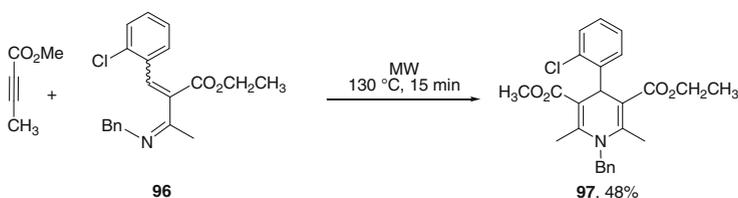
Scheme 2.68 Aza-Diels–Alder cycloaddition to form an 1,4-dihydropyridine derivative

The MW-assisted [4+2] cycloadditions for the synthesis of drug-like heterocycles was also reported. The [4+2] cycloaddition of 1,4-diaryl-1-aza-1,3-butadienes (**98**) with allenic esters at 100 °C followed by a tandem 1,3-H-shift provided 1,4-dihydropyridines (**100**) in excellent, 83–96 % yields (Scheme 2.69). Comparative thermal reactions required 33–76 h resulting in lower yields [106]. The unsymmetrically substituted 1,4-dihydropyridines (**100**) obtained are well-known for their potential biological activities.
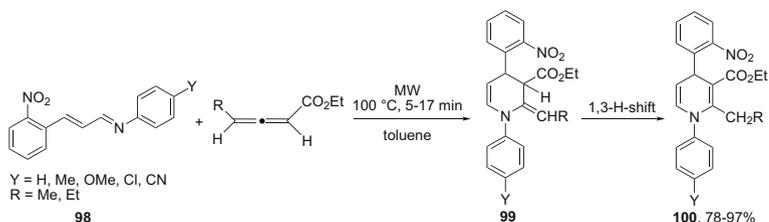
Scheme 2.69 MW-assisted synthesis of unsymmetrically substituted 1,4-dihydropyridines

2.5 Conclusions

In summary, MW-assisted coupling reactions, condensations, multicomponent reactions and cycloadditions providing an access to a wide variety of different scaffolds were presented. In all cases, MW irradiation led to shorter reaction times and higher yields in comparison with conventional heating, or even promoted reactions that were unsuccessful on conventional conditions.

References

1. Gupta AK, Singh N, Singh KN (2015) On water synthesis of highly functionalized 4Hchromenes via carbon–carbon bond formation under microwave irradiation and their antibacterial properties. Curr Org Chem 5:28958–28964. doi:10.1039/c5ra01301a
2. Allam BK, Singh KN (2011) An efficient phosphine-free heck reaction in water using Pd (l-proline)2 as the catalyst under microwave irradiation. Synthesis 2011:1125–1131. doi:10.1055/s-0030-1258452
3. Herve G, Len C (2014) First ligand-free, microwave-assisted, Heck cross-coupling reaction in pure water on a nucleoside—application to the synthesis of antiviral BVDU. RSC Adv 4:46926–46929. doi:10.1039/C4RA09798J
4. Len C, Hervé G (2015) Aqueous microwaves assisted cross-coupling reactions applied to unprotected nucleosides. Front Chem 3:10. doi:10.3389/fchem.2015.00010
5. Dighe MG, Degani MS (2011) Microwave-assisted ligand-free, base-free Heck reactions in a task-specific imidazolium ionic liquid. Arkivoc XI:189–197. doi:10.3998/ark.5550190.0012.b17
6. Bai L, Wang J-X, Zhang Y (2003) Rapid microwave-promoted Suzuki cross coupling reaction in water. Green Chem 5:615–617. doi:10.1039/B305191A
7. Crozet MD, Castera-Ducros C, Vanelle P (2006) An efficient microwave-assisted Suzuki cross-coupling reaction of imidazo[1,2-a]pyridines in aqueous medium. Tetrahedron Lett 47:7061–7065. doi:10.1016/j.tetlet.2006.07.098
8. Dawood KM, El-Deftar MM (2010) Microwave-assisted C-C cross-coupling reactions of aryl and heteroaryl halides in water. Arkivoc 9:319–330. doi:10.3998/ark.5550190.0011.930
9. Cohen A, Crozet MD, Rathelot P, Vanelle P (2009) An efficient aqueous microwave-assisted Suzuki-Miyaura cross-coupling reaction in the thiazole series. Green Chem 11:1736–1742. doi:10.1039/B916123F
10. Saha P, Naskar S, Paira P, Hazra A, Sahu KB, Paira R, Banerjee S, Mondal NB (2009) Basic alumina-supported highly effective Suzuki-Miyaura cross-coupling reaction under microwave irradiation: application to fused tricyclic oxa-aza-quinolones. Green Chem 11:931–934. doi:10.1039/B902916H
11. Baghbanzadeh M, Pilger C, Kappe CO (2011) Rapid nickel-catalyzed Suzuki–Miyaura cross-couplings of aryl carbamates and sulfamates utilizing microwave heating. J Org Chem 76:1507–1510. doi:10.1021/jo1024464
12. Yılmaz Ü, Küçükbay H, Şireci N, Akkurt M, Günal S, Durmaz R, Nawaz Tahir M (2011) Synthesis, microwave-promoted catalytic activity in Suzuki-Miyaura cross-coupling reactions and antimicrobial properties of novel benzimidazole salts bearing trimethylsilyl group. Appl Organomet Chem 25:366–373. doi:10.1002/aoc.1772
13. Gupta AK, Singh N, Singh KN (2013) Microwave assisted organic synthesis: cross coupling and multicomponent reactions. Curr Org Chem 17:474–490. doi:10.2174/1385272811317050005

14. Shah D, Kaur H (2012) Macroporous resin impregnated palladium nanoparticles: Catalyst for a microwave-assisted green Hiyama reaction. J Mol Catal A: Chem 359:69–73. doi:10.1016/j.molcata.2012.03.022

15. Gupta AK, Tirumaleswara Rao G, Singh KN (2012) NiCl2·6H2O as recyclable heterogeneous catalyst for N-arylation of amines and NH-heterocycles under microwave exposure. Tetrahedron Lett 53:2218–2221. doi:10.1016/j.tetlet.2012.02.081

16. Guo D, Huang H, Zhou Y, Xu J, Jiang H, Chen K, Liu H (2010) Ligand-free iron/copper cocatalyzed N-arylations of aryl halides with amines under microwave irradiation. Green Chem 12:276–281. doi:10.1039/B917010C

17. Liu Z-J, Vors J-P, Gesing ERF, Bolm C (2011) Microwave-assisted solvent- and ligand-free copper-catalysed cross-coupling between halopyridines and nitrogen nucleophiles. Green Chem 13:42–45. doi:10.1039/C0GC00296H

18. Chow WS, Chan TH (2009) Microwave-assisted solvent-free N-arylation of imidazole and pyrazole. Tetrahedron Lett 50:1286–1289. doi:10.1016/j.tetlet.2008.12.119

19. Hirao T, Masunaga T, Ohshiro Y, Agawa T (1980) Stereoselective synthesis of vinylphosphonate. Tetrahedron Lett 21:3595–3598. doi:10.1016/0040-4039(80)80245-0

20. Kalek M, Ziadi A, Stawinski J (2008) Microwave-assisted palladium-catalyzed cross-coupling of aryl and vinyl halides with H-phosphonate diesters. Org Lett 10:4637–4640. doi:10.1021/ol801935r

21. Jiang W, Allan G, Fiordeliso JJ, Linton O, Tannenbaum P, Xu J, Zhu P, Gunnet J, Demarest K, Lundeen S, Sui Z (2006) New progesterone receptor antagonists: phosphorus-containing 11β-aryl-substituted steroids. Bioorg Med Chem 14:6726–6732. doi:10.1016/j.bmc.2006.05.066

22. Andaloussi M, Lindh J, Sävmarker J, Sjöberg PJR, Larhed M (2009) Microwave-promoted palladium(II)-catalyzed C–P bond formation by using arylboronic acids or aryltrifluoroborates. Chem Eur J 15:13069–13074. doi:10.1002/chem.200901473

23. Julienne D, Lohier J-F, Delacroix O, Gaumont A-C (2007) Palladium-catalyzed C–P coupling reactions between vinyl triflates and phosphine–boranes: Efficient access to vinylphosphine–boranes. J Org Chem 72:2247–2250. doi:10.1021/jo062482o

24. Jablonkai E, Keglevich G (2013) P-ligand-free, microwave-assisted variation of the Hirao reaction under solvent-free conditions; the P-C coupling reaction of >P(O)H species and bromoarenes. Tetrahedron Lett 54:4185–4188. doi:10.1016/j.tetlet.2013.05.111

25. Jablonkai E, Keglevich G (2014) Advances and new variations of the Hirao reaction. Org Prep Proced Int 46:281–316. doi:10.1080/00304948.2014.922376

26. Kohler MC, Sokol JG, Stockland RA Jr (2009) Development of a room temperature Hirao reaction. Tetrahedron Lett 50:457–459. doi:10.1016/j.tetlet.2008.11.040

27. Bagley M, Lubinu MC (2006) Microwave-assisted multicomponent reactionsfor the synthesis of heterocycles. In: Van der Eycken E, Kappe CO (eds) Microwave-assisted synthesis of heterocycles, vol 1. Topics in Heterocyclic Chemistry. Springer, Berlin, pp 31–58. doi:10.1007/7081_004

28. Marjani K, Asgari M, Ashouri A, Mahdavinia GH, Ahangar HA (2009) Microwave-assisted aldol condensation of benzil with ketones. Chin Chem Lett 20:401–403. doi:10.1016/j.cclet.2008.12.036

29. Zhang C, Wang B-S, Chen S-F, Zhang S-Q, Cui D-M (2011) Synthesis of 3-methyl-2-cyclohexenones catalyzed by mercury(II) salts and their microwave assisted BiCl3 catalyzed aldol condensations. J Organomet Chem 696:165–169. doi:10.1016/j.jorganchem.2010.08.037

30. Claisen L, Claparède A (1881) Condensationen von Ketonen mit Aldehyden. Ber Dtsch Chem Ges 14:2460–2468. doi:10.1002/cber.188101402192

31. Min-yi L, Dan W, Zhi-xiong L (2009) Synthesis of tert-butyl-methoxy-dibenzoylmethane under microwave irradiation. Chin Surf Det Cosm 39:179–182

32. Knoevenagel E (1898) Condensation von Malonsäure mit aromatischen Aldehyden durch Ammoniak und Amine. Ber Dtsch Chem Ges 31:2596–2619. doi:10.1002/cber.18980310308

33. Ansari MB, Jin H, Parvin MN, Park S-E (2012) Mesoporous carbon nitride as a metal-free base catalyst in the microwave assisted Knoevenagel condensation of ethylcyanoacetate with aromatic aldehydes. Catal Today 185:211–216. doi:10.1016/j.cattod.2011.07.024

34. Sundaram K, Ravi S (2013) Microwave-assisted synthesis of 3-α-carboxyethylrhodanine derivatives and their in vitro antibacterial activity. J Appl Pharm Sci 3:133–135. doi:10.7324/JAPS.2013.3725

35. Biradar JS, Sasidhar BS (2011) Solvent-free, microwave assisted Knoevenagel condensation of novel 2,5-disubstituted indole analogues and their biological evaluation. Eur J Med Chem 46:6112–6118. doi:10.1016/j.ejmech.2011.10.004

36. Mannich C, Krösche W (1912) Ueber ein kondensationsprodukt aus formaldehyd, ammoniak und antipyrin. Arch Pharm 250:647–667. doi:10.1002/ardp.19122500151

37. Sankappa Rai U, Isloor AM, Shetty P, Isloor N, Malladi S, Fun H-K (2010) Synthesis and biological evaluation of aminoketones. Eur J Med Chem 45:6090–6094. doi:10.1016/j.ejmech.2010.09.015

38. Lehmann F, Pilotti Å, Luthman K (2003) Efficient large scale microwave assisted Mannich reactions using substituted acetophenones. Mol Divers 7:145–152. doi:10.1023/B:MODI.0000006809.48284.ed

39. Leadbeater N, Torenius H, Tye H (2003) Microwave-assisted Mannich-type three-component reactions. Mol Divers 7:135–144. doi:10.1023/B:MODI.0000006822.51884.e6

40. Dong X, Liu T, Chen J, Ying H, Hu Y (2009) Microwave-assisted Mannich reaction of 2-hydroxy-chalcones. Synth Commun 39:733–742. doi:10.1080/00397910802431107

41. Biginelli P (1891) Ueber aldehyduramide des acetessigäthers. Ber Dtsch Chem Ges 24:1317–1319. doi:10.1002/cber.189102401228

42. Kappe CO (2000) Biologically active dihydropyrimidones of the Biginelli-type—a literature survey. Eur J Med Chem 35:1043–1052. doi:10.1016/S0223-5234(00)01189-2

43. Kumar PBR, Sankar G, Nasir Baig RB, Chandrashekaran S (2009) Novel Biginelli dihydropyrimidines with potential anticancer activity: a parallel synthesis and CoMSIA study. Eur J Med Chem 44:4192–4198. doi:10.1016/j.ejmech.2009.05.014

44. Ranjith C, Srinivasan GV, Vijayan KK (2010) Tributyl borate mediated Biginelli reaction: a facile microwave-assisted green synthetic strategy toward dihydropyrimidinones. Bull Chem Soc Jpn 83:288–290. doi:10.1002/chin.201029176

45. Fu R, Yang Y, Lai W, Ma Y, Chen Z, Zhou J, Chai W, Wang Q, Yuan R (2015) Efficient and green microwave-assisted multicomponent Biginelli reaction for the synthesis of dihydropyrimidinones catalyzed by heteropolyanion-based ionic liquids under solvent-free conditions. Synth Commun 45:467–477. doi:10.1080/00397911.2014.976346

46. Virsodia VR, Vekariya NR, Manvar AT, Khunt RC, Marvania BR, Savalia BS, Shah AK (2008) Catalyst-free, rapid synthesis of fused bicyclic thiazolo-pyrimidine and pyrimido-thiazine derivatives by a microwave-assisted method. Phosphorus Sulfur Silicon Relat Elem 184:34–44. doi:10.1080/10426500802077564

47. Fang Z, Lam Y (2011) A rapid and convenient synthesis of 5-unsubstituted 3,4-dihydropyrimidin-2-ones and thiones. Tetrahedron 67:1294–1297. doi:10.1016/j.tet.2010.11.075

48. Legeay J-C, Vanden Eynde JJ, Bazureau JP (2005) Ionic liquid phase technology supported the three component synthesis of Hantzsch 1,4-dihydropyridines and Biginelli 3,4-dihydropyrimidin-2(1H)-ones under microwave dielectric heating. Tetrahedron 61:12386–12397. doi:10.1016/j.tet.2005.09.118

49. Hantzsch A (1881) Condensationsprodukte aus aldehydammoniak und ketonartigen verbindungen. Ber Dtsch Chem Ges 14:1637–1638. doi:10.1002/cber.18810140214

50. Öhberg L, Westman J (2001) An Efficient and fast procedure for the Hantzsch dihydropyridine synthesis under microwave conditions. Synlett 2001:1296–1298. doi:10.1055/s-2001-16043

51. Bandyopadhyay D, Maldonado S, Banik BK (2012) A microwave-assisted bismuth nitrate-catalyzed unique route toward 1,4-dihydropyridines. Molecules 17:2643–2662. doi:10.3390/molecules17032643

52. Kar P, Mishra BG (2013) Silicotungstic acid nanoparticles dispersed in the micropores of Cr-pillared clay as efficient heterogeneous catalyst for the solvent free synthesis of 1,4-dihydropyridines. Chem Eng J 223:647–656. doi:10.1016/j.cej.2013.03.050

53. Bucherer HT, Fischbeck HT (1934) J Prakt Chem 140:69

54. Bergs H (1933) Chem Abstr 27:1001

55. Safari J, Gandomi-Ravandi S, Javadian L (2013) Microwave-promoted facile and rapid synthesis procedure for the efficient synthesis of 5,5-disubstituted hydantoins. Synth Commun 43:3115–3120. doi:10.1080/00397911.2012.730647

56. Handzlik J, Bojarski AJ, Satała G, Kubacka M, Sadek B, Ashoor A, Siwek A, Więcek M, Kucwaj K, Filipek B, Kieć-Kononowicz K (2014) SAR-studies on the importance of aromatic ring topologies in search for selective 5-HT7 receptor ligands among phenylpiperazine hydantoin derivatives. Eur J Med Chem 78:324–339. doi:10.1016/j. ejmech.2014.01.065

57. Strecker A (1854) Ueber einen neuen aus aldehyd—ammoniak und blausäure entstehenden körper. Justus Liebigs Ann Chem 91:349–351. doi:10.1002/jlac.18540910309

58. Prakash GKS, Bychinskaya I, Marinez ER, Mathew T, Olah GA (2013) Nafion–Fe: a new efficient "green" lewis acid catalyst for the ketonic strecker reaction. Catal Lett 143:303–312. doi:10.1007/s10562-012-0958-2

59. Rajabi F, Nourian S, Ghiassian S, Balu AM, Saidi MR, Serrano-Ruiz JC, Luque R (2011) Heterogeneously catalysed Strecker-type reactions using supported Co(ii) catalysts: microwave versus conventional heating. Green Chem 13:3282–3289. doi:10.1039/c1gc15741h

60. Das D, Richers MT, Ma L, Seidel D (2011) The decarboxylative Strecker reaction. Org Lett 13:6584–6587. doi:10.1021/ol202957d

61. Gewald K, Schinke E, Böttcher H (1966) Heterocyclen aus CH-aciden nitrilen, VIII. 2-Amino-thiophene aus methylenaktiven nitrilen, carbonylverbindungen und schwefel. Chem Ber 99:94–100. doi:10.1002/cber.19660990116

62. Revelant G, Dunand S, Hesse S, Kirsch G (2011) Microwave-assisted synthesis of 5-substituted 2-aminothiophenes starting from arylacetaldehydes. Synthesis 2011:2935–2940. doi:10.1055/s-0030-1261032

63. Sridhar M, Rao RM, Baba NHK, Kumbhare RM (2007) Microwave accelerated Gewald reaction: synthesis of 2-aminothiophenes. Tetrahedron Lett 48:3171–3172. doi:10.1016/j. tetlet.2007.03.052

64. Kunda PK, Rao JV, Mukkanti K, Induri M, Reddy GD (2013) Synthesis, anticonvulsant activity and in silco studies of schiff bases of 2-aminothiophenes via guanidine catalyzed Gewald reaction. Trop J Pharm Res 12:566–576. doi:10.4314/tjpr.v12i4.19

65. Zhang H, Yang G, Chen J, Chen Z (2004) Synthesis of thiophene derivatives on soluble polymer-support using Gewald reaction. Synthesis 2004:3055–3059. doi:10.1055/s-2004-834895

66. Fields EK (1952) The synthesis of esters of substituted amino phosphonic acids. J Am Chem Soc 74:1528–1531. doi:10.1021/ja01126a054

67. Kabachnik Martin I, Medved TY (1952) A new method for the synthesis of α-amino phosphoric acids. Dokl Akad Nauk SSSR 83:689

68. Mu X-J, Lei M-Y, Zou J-P, Zhang W (2006) Microwave-assisted solvent-free and catalyst-free Kabachnik-Fields reactions for α-amino phosphonates. Tetrahedron Lett 47:1125–1127. doi:10.1016/j.tetlet.2005.12.027

69. Tibhe GD, Reyes-González MA, Cativiela C, Ordóñez M (2012) Microwave-assisted high diastereoselective synthesis of α-aminophosphonates under solvent and catalyst free-conditions. J Mex Chem Soc 56:183–187

70. Gangireddy CSR, Chinthaparthi RR, Mudumala VNR, Cirandur SR (2014) An elegant microwave assisted one-pot synthesis of di(α-aminophosphonate) pesticides. Arch Pharm 347:819–824. doi:10.1002/ardp.201400213

71. Kindler K (1923) Studien über den mechanismus chemischer reaktionen. Erste abhandlung. Reduktion von amiden und oxydation von aminen. Justus Liebigs Ann Chem 431:187–230. doi:10.1002/jlac.19234310111

72. Agnimonhan FH, Ahoussi L, Kpoviessi SDS, Gbaguidi FA, Kapanda CN, Moudachirou M, Poupaert J, Accrombessi GC (2014) Comparative study of acid and basic catalysis in microwave assistance of Willgerodt-Kindler reaction for thiobenzamides and derivatives synthesis. Int J Biol Chem Sci 8:386–393. doi:10.4314/ijbcs.v8i1.32

73. Zbruyev OI, Stiasni N, Kappe CO (2003) Preparation of thioamide building blocks via microwave-promoted three-component Kindler reactions. J Comb Chem 5:145–148. doi:10.1021/cc0200538

74. Passerini M, Simone L (1921) Gazz Chim Ital 51:126–129

75. Barreto AFS, Vercillo OE, Andrade CKZ (2011) Microwave-assisted Passerini reactions under solvent-free conditions. J Brazil Chem Soc 22:462–467. doi:10.1590/S0103-50532011000300008

76. Chai C-C, Liu P-Y, Lin C-H, Chen H-C, Wu Y-C, Chang F-R, Pan P-S (2013) Efficient synthesis of boron-containing α-acyloxyamide analogs via microwave irradiation. Molecules 18:9488–9511. doi:10.3390/molecules18089488

77. Ingold M, López GV, Porcal W (2014) Green conditions for Passerini three-component synthesis of tocopherol analogues. ACS Sustainable Chem Eng 2:1093–1097. doi:10.1021/sc5002116

78. Ugi I, Meyr R, Fetzer U, Steinbrückner C (1959) Versuche mit isonitrilen. Angew Chem 71:386. doi:10.1002/ange.19590711110

79. Xing X, Wu J, Feng G, Dai W-M (2006) Microwave-assisted one-pot U-4CR and intramolecular O-alkylation toward heterocyclic scaffolds. Tetrahedron 62:6774–6781. doi:10.1016/j.tet.2006.05.001

80. Tye H, Whittaker M (2004) Use of a Design of Experiments approach for the optimisation of a microwave assisted Ugi reaction. Org Biomol Chem 2:813–815. doi:10.1039/b400298a

81. Jida M, Malaquin S, Deprez-Poulain R, Laconde G, Deprez B (2010) Synthesis of five- and six-membered lactams via solvent-free microwave Ugi reaction. Tetrahedron Lett 51:5109–5111. doi:10.1016/j.tetlet.2010.07.021

82. Jiang B, Wang X, Shi F, Tu S-J, Ai T, Ballew A, Li G (2009) Microwave enabled umpolung mechanism based rapid and efficient four- and six-component domino formations of 2-(2′-azaaryl)imidazoles and anti-1,2-diarylethylbenzamides. J Org Chem 74:9486–9489. doi:10.1021/jo902204s

83. Kulkarni A, Torok B (2010) Microwave-assisted multicomponent domino cyclization-aromatization: an efficient approach for the synthesis of substituted quinolines. Green Chem 12:875–878. doi:10.1039/c001076f

84. Appukkuttan P, Mehta VP, Van der Eycken EV (2010) Microwave-assisted cycloaddition reactions. Chem Soc Rev 39:1467–1477. doi:10.1039/B815717K

85. Bougrin K, Benhida R (2012) Microwave-assisted cycloaddition reactions. In: Microwaves in organic synthesis. Wiley-VCH, Verlag, pp 737–809. doi:10.1002/9783527651313.ch17

86. Ovaska TV, Kyne RE (2008) Intramolecular thermal allenyne [2+2] cycloadditions: facile construction of the 5–6–4 ring core of sterpurene. Tetrahedron Lett 49:376–378. doi:10.1016/j.tetlet.2007.11.042

87. Brummond KM, Chen D (2005) Microwave-Assisted Intramolecular [2+2] Allenic Cycloaddition Reaction for the Rapid Assembly of Bicyclo[4.2.0]octa-1,6-dienes and Bicyclo[5.2.0]nona-1,7-dienes. Org Lett 7:3473–3475. doi:10.1021/ol051115g

88. Hu L, Wang Y, Li B, Du D-M, Xu J (2007) Diastereoselectivity in the Staudinger reaction: a useful probe for investigation of nonthermal microwave effects. Tetrahedron 63:9387–9392. doi:10.1016/j.tet.2007.06.112

89. Uršič U, Grošelj U, Meden A, Svete J, Stanovnik B (2008) Regiospecific [2+2] cycloadditions of electron-poor acetylenes to (Z)-2-acylamino-3-dimethylaminopropenoates: synthesis of highly functionalised buta-1,3-dienes. Tetrahedron Lett 49:3775–3778. doi:10.1016/j.tetlet.2008.04.021

90. Johnstone MD, Lowe AJ, Henderson LC, Pfeffer FM (2010) Rapid synthesis of cyclobutene diesters using a microwave-accelerated ruthenium-catalysed [2+2] cycloaddition. Tetrahedron Lett 51:5889–5891. doi:10.1016/j.tetlet.2010.08.119

91. Himo F, Lovell T, Hilgraf R, Rostovtsev VV, Noodleman L, Sharpless KB, Fokin VV (2005) Copper(I)-catalyzed synthesis of azoles. DFT Study predicts unprecedented reactivity and intermediates. J Am Chem Soc 127:210–216. doi:10.1021/ja0471525

92. Moorhouse AD, Moses JE (2008) Microwave enhancement of a 'one-pot' tandem azidation-'click' cycloaddition of anilines. Synlett 2008:2089–2092. doi:10.1055/s-2008-1078019

93. Taher A, Nandi D, Islam RU, Choudhary M, Mallick K (2015) Microwave assisted azide-alkyne cycloaddition reaction using polymer supported Cu(i) as a catalytic species: a solventless approach. RSC Adv 5:47275–47283. doi:10.1039/C5RA04490A

94. Rasmussen LK, Boren BC, Fokin VV (2007) Ruthenium-catalyzed cycloaddition of aryl azides and alkynes. Org Lett 9:5337–5339. doi:10.1021/ol701912s

95. Louërat F, Bougrin K, Loupy A, Ochoa de Retana AM, Pagalday J, Palacios F (1998) Cycloaddition reactions of azidomethyl phosphonate with acetylenes and enamines. Synthesis of triazoles. Heterocycles 48:161–170. doi:10.3987/COM-97-7997

96. Cantillo D, Gutmann B, Kappe CO (2011) Mechanistic insights on azide–nitrile cycloadditions: on the dialkyltin oxide–trimethylsilyl azide route and a new Vilsmeier–Haack-type organocatalyst. J Am Chem Soc 133:4465–4475. doi:10.1021/ja109700b

97. Díaz-Ortiz Á, de Cózar A, Prieto P, de la Hoz A, Moreno A (2006) Recyclable supported catalysts in microwave-assisted reactions: first Diels-Alder cycloaddition of a triazole ring. Tetrahedron Lett 47:8761–8764. doi:10.1016/j.tetlet.2006.10.006

98. Zheng S, Chowdhury A, Ojima I, Honda T (2013) Microwave-assisted Diels-Alder reactions between Danishefsky's diene and derivatives of ethyl α-(hydroxymethyl)acrylate. Synthetic approach toward a biotinylated anti-inflammatory monocyclic cyanoenone. Tetrahedron 69:2052–2055. doi:10.1016/j.tet.2012.12.079

99. Petronijevic F, Timmons C, Cuzzupe A, Wipf P (2008) A microwave assisted intramolecular-furan-Diels-Alder approach to 4-substituted indoles. Chem Commun 1:106. doi:10.1039/B816989F

100. Kranjc K, Kočevar M (2008) An expedient route to indoles via a cycloaddition/cyclization sequence from (Z)-1-methoxybut-1-en-3-yne and 2H-pyran-2-ones. Tetrahedron 64:45–52. doi:10.1016/j.tet.2007.10.099

101. Gómez VM, Aranda AI, Moreno A, Cossío FP, de Cózar A, Díaz-Ortiz Á, de la Hoz A, Prieto P (2009) Microwave-assisted reactions of nitroheterocycles with dienes. Diels-Alder and tandem hetero Diels–Alder/[3,3] sigmatropic shift. Tetrahedron 65:5328–5336. doi:10.1016/j.tet.2009.04.065

102. Benedetti E, Kocsis LS, Brummond KM (2012) Synthesis and photophysical properties of a series of cyclopenta[b]naphthalene solvatochromic fluorophores. J Am Chem Soc 134:12418–12421. doi:10.1021/ja3055029

103. Brummond KM, Kocsis LS (2015) Intramolecular didehydro-Diels–Alder reaction and its impact on the structure–function properties of environmentally sensitive fluorophores. Acc Chem Res 48:2320–2329. doi:10.1021/acs.accounts.5b00126

104. Hajbi Y, Suzenet F, Khouili M, Lazar S, Guillaumet G (2007) Polysubstituted 2,3-dihydrofuro[2,3-b]pyridines and 3,4-dihydro-2H-pyrano[2,3-b]pyridines via microwave-activated inverse electron demand Diels-Alder reactions. Tetrahedron 63:8286–8297. doi:10.1016/j.tet.2007.05.112

105. Lee YA, Kim SC (2011) Synthesis of 1,4-dihydropyridine using microwave-assisted aza-Diels–Alder reaction and its application to Amlodipine. J Ind Eng Chem 17:401–403. doi:10.1016/j.jiec.2011.02.031

106. Singh L, Singh Ishar MP, Elango M, Subramanian V, Gupta V, Kanwal P (2008) Synthesis of unsymmetrical substituted 1,4-dihydropyridines through thermal and microwave assisted [4+2] cycloadditions of 1-azadienes and allenic esters. J Org Chem 73:2224–2233. doi:10.1021/jo702548b