Microwave-assisted heterocyclic synthesis[‡]

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Abstract
Recent applications of microwave technology in well-known cyclization reactions for heterocyclic ring formation and in other important reactions such as nucleophilic substitution, hetero-Diels–Alder reactions, 1,3-dipolar cycloaddition etc. have been discussed. A comparison with the conventional methods demonstrates the advantages of microwaves in synthetic heterocyclic chemistry.

Keywords: Heterocycles, conventional heating, microwaves, single-mode technology

Contents

Introduction

Microwave heating has emerged as a powerful technique to promote a variety of chemical reactions.[1] Microwave reactions under solvent-free conditions are attractive in offering reduced pollution and offer low cost together with simplicity in processing and handling.[2] The recent introduction of single-mode technology[3] assures safe and reproducible experimental procedures and microwave synthesis has gained acceptance and popularity among the synthetic chemist community. The growing number of publications in microwave-assisted synthesis includes virtually all types of chemical reactions such as additions, cycloadditions, substitutions, eliminations, fragmentations etc.[3]

In the present short review, we are trying to highlight some of the applications of microwave methodology in heterocyclic chemistry. The graphic enhancements in the speed of reactions and in yields are striking. Undoubtedly, microwaves are going to be highly important in future synthesis of heterocycles. Bearing in mind that most biologically active compounds are heterocyclic and the importance in combinatorial chemistry to identify leads and to optimize structures, we believe that the number of applications of microwaves will only increase in the future. The present review is organized to emphasize some of the most important areas that have so far been identified.

1. Applications of microwaves in heterocyclic ring formation

1.1. Five-membered heterocyclic rings

1.1.1. Pyrroles

The classical Paal-Knorr cyclization of 1,4-diketones to give pyrroles is dramatically speeded-up under microwave irradiation and high yields are obtained as shown in Scheme 1.[4]

$R = CH_2C_6H_5,$
4-MeOC$_6$H$_4$,
2-ClC$_6$H$_4$ etc.

75-90%
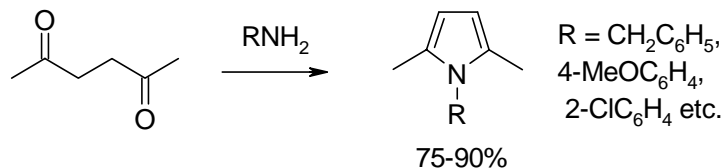
MW, 100-200 W, 0.5-2.0 min., solvent-free

Microwave: 2 min.
Conventional: Lewis acid activation, 12h.

Scheme 1

1.1.2. Pyrazoles

Another recent application of microwaves in cyclization is the preparation of pyrazoles from hydrazones using the Vilsmeier cyclization method by treatment with POCl$_3$ and DMF.[5] As shown in Scheme 2, once again the reaction is speeded-up by factors of several 100-fold.

POCl$_3$

MW, 210 W, 30-50 sec., DMF

Microwave: 35-50 sec., 45-78%
Conventional: 4-5 h, 41-76%

$R^1 = H, OH; R^2 = H, CH_3;$
$R^3 = H, NO_2; R^4 = NO_2;$
$R^5 = CH_3, C_2H_5$
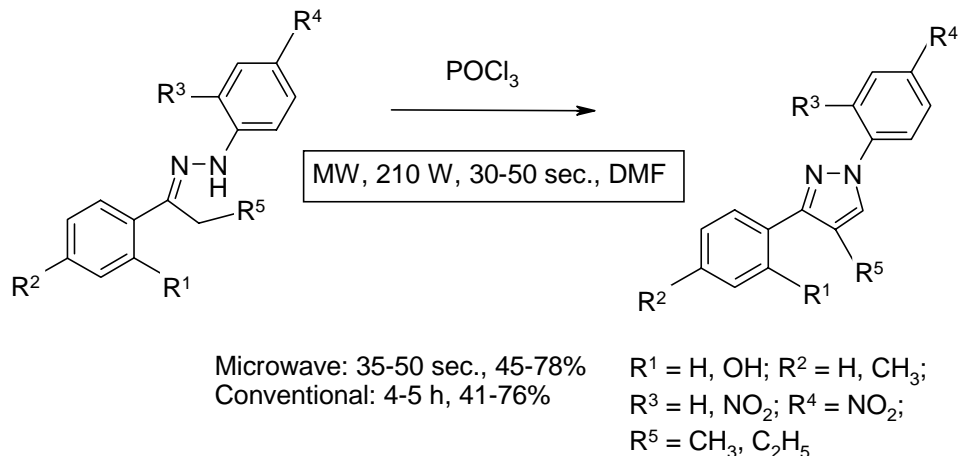
Scheme 2

1.1.3. Imidazoles

An important classical preparation of imidazoles is from an α-diketone, an aldehyde and ammonia. Here again, excellent yields can be obtained in reaction times of a few minutes as shown in Scheme 3.[6]

MW, 130 W, 10 min., solvent-free

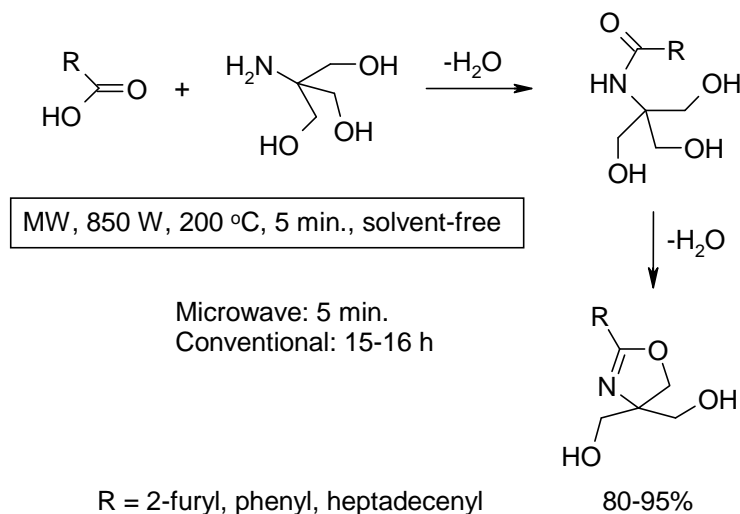75-85%

Microwave: 10 min.
Conventional: 4 h, AcOH reflux

$R^1 = C_6H_5$, 4-ClC_6H_4,
2-thiophenyl etc.
$R^2 = R^3 = C_6H_5$, 4-MeC_6H_4
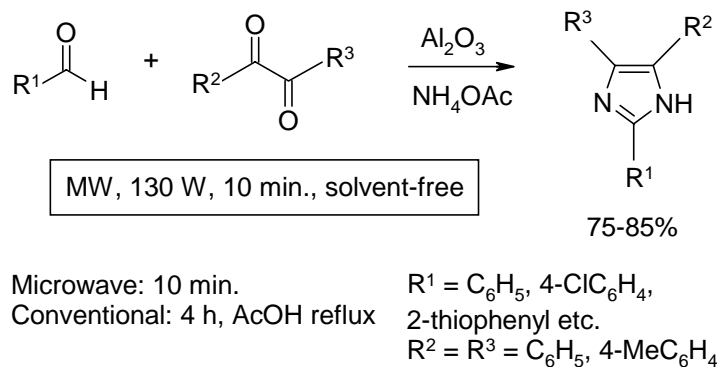
Scheme 3

1.1.4. Oxazolines

The example of Scheme 4, the preparation of oxazolines shows that partially saturated five-membered rings can also be prepared advantageously using microwaves.[7]

MW, 850 W, 200 °C, 5 min., solvent-free

Microwave: 5 min.
Conventional: 15-16 h

-H_2O

R = 2-furyl, phenyl, heptadecenyl   80-95%

Scheme 4

1.1.5. Triazoles and Tetrazoles

Schemes 5 and 6 continue the overview of five-membered rings with illustrations of the advantageous preparation of 1,2,4–triazoles (Scheme 5)[8] and tetrazoles (Scheme 6)[9] using microwaves. Notice that in Scheme 6 the starting aryl cyanides are also made by a Pd-catalyzed but microwave-enhanced replacement of aryl bromides using zinc cyanide.

$$Ar—C≡N \xrightarrow[\text{H}_2\text{N-NH}_2.\text{H}_2\text{O}]{\text{H}_2\text{N-NH}_2.2\text{HCl}}$$
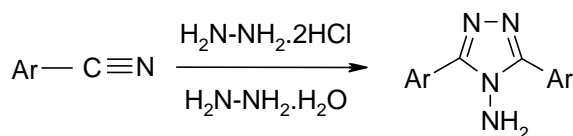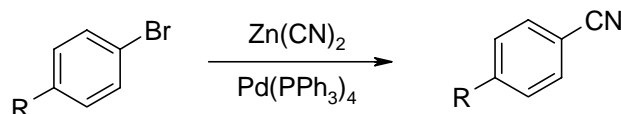
MW, 60 W, 130 °C, 4-10 min., ethylene glycol

Microwave: 10 min., 130 °C, 63-96%   Ar = C_6H_5, 4-$CH_3C_6H_4$,
Conventional: 60 min., 130 °C, 45-60%   4-$NH_2C_6H_4$, 4-OHC_6H_4,
                                                                      4-$CH_3OC_6H_4$ etc.

Scheme 5

$$\xrightarrow[\text{Pd(PPh}_3)_4]{\text{Zn(CN)}_2}$$

MW, 60 W, 175 °C, 2 min., DMF

Microwave: 2 min., 78-93%
Conventional: 2-16 h, 71-97%

NaN_3
NH_4Cl
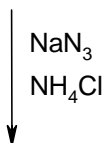
MW, 20 W, 220 °C, 10-25 min., DMF

Microwave: 10-25 min., 36-96%
Conventional: 3-96 h, 35-97%   R = OCH_3, NO_2, CH_3 etc.
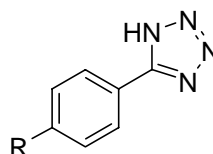
Scheme 6

1.1.6. Oxadiazoles

The dehydration of unsymmetrical diacylhydrazines (themselves prepared by a conventional Mitsunobu reaction) using Burgess's reagent is shown in Scheme 7 to give 1,3,4-oxadiazoles rapidly under microwave irradiation.[3]

MW, 5-10 min., DMF
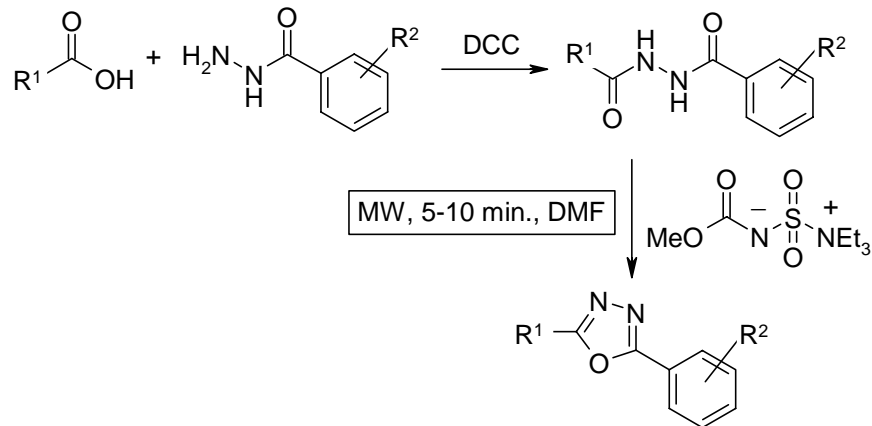
Microwave: 5-10 min., 150 °C   100%
Conventional: 90 min., 150 °C R^1 = alkyl, aryl; R^2 = Cl, OMe

Scheme 7

1.1.7. Isoxazolines and pyrazolines

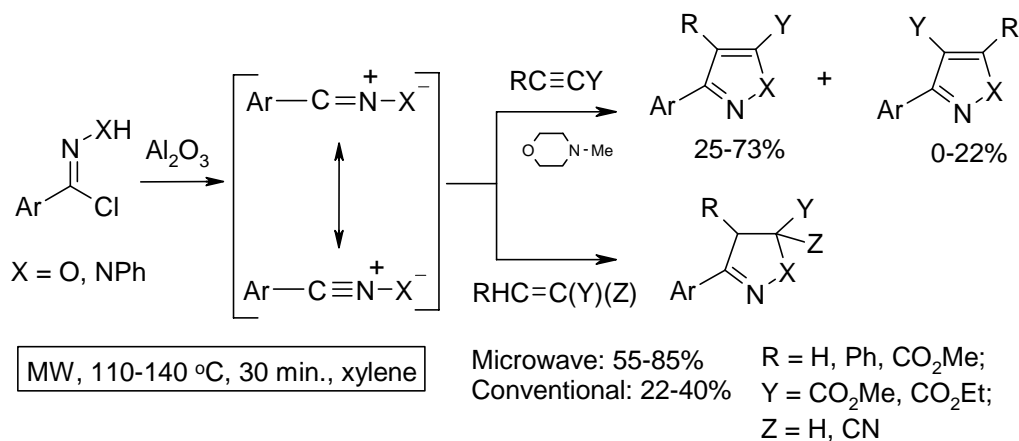The acceleration of 1,3-dipolar cycloaddition reactions to give isoxazolines and pyrazolines by the addition of activated olefins to nitrile oxides or nitrile imides, respectively, is illustrated in Scheme 8; the resulting compounds are obtained in far high yield than under conventional conditions.[10]

Scheme 8

1.2. Benzo-derivatives of five-membered rings

1.2.1. Benz-imidazoles, -oxazoles, and -thiazoles

Ring closure reactions of appropriate *o*-substituted anilines to give benzimidazoles, benzoxazoles, and benzthiazoles takes place much faster and in significantly high yield under microwave conditions[11a] than conventionally[11b] as shown in Scheme 9.
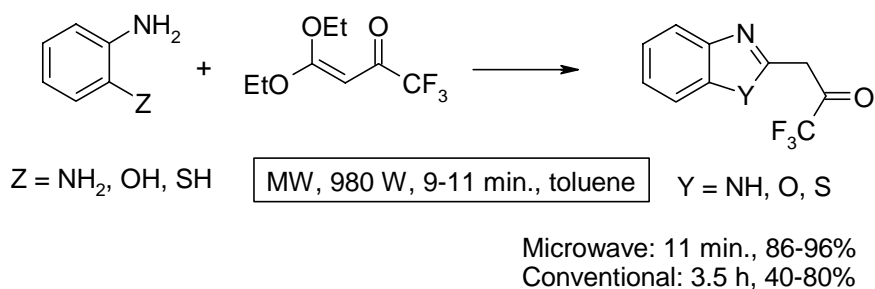
Scheme 9

1.2.2. Indoles

The classical Fischer-indole synthesis from an aryl hydrazine and a ketone is speeded-up by several 100-fold as documented in Scheme 10.[12]

Scheme 10

1.2.3. γ-Carbolines

The Graebe-Ullmann synthesis which converts 1-arylbenzotriazoles into carbazoles or their heterocyclic analogs is also accelerated under microwave conditions as shown in Scheme 11 where the 1-(4-pyridyl)benzotriazole is converted into a γ-carboline.[13]
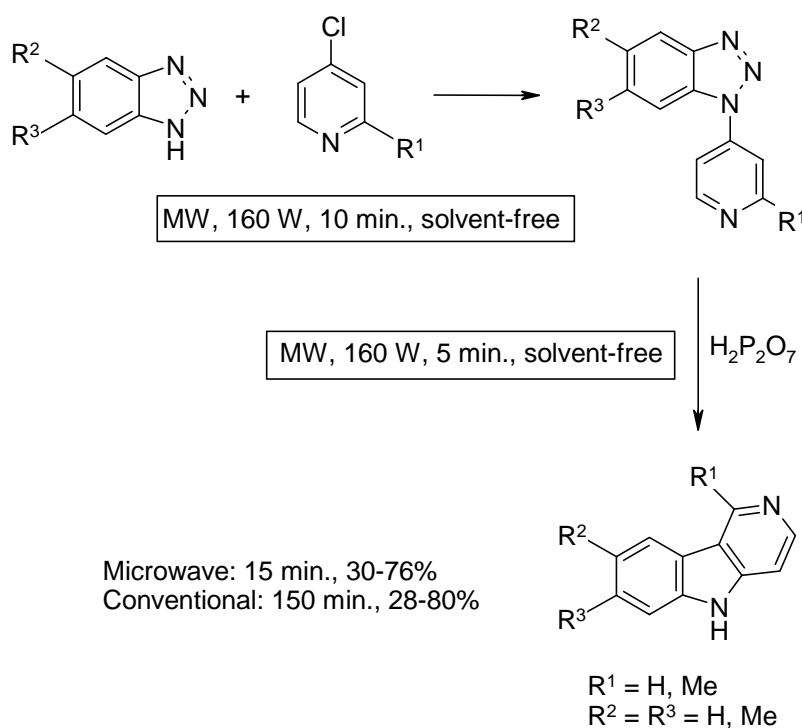
Scheme 11

1.3. Six-membered rings
1.3.1. Dihydropyridines

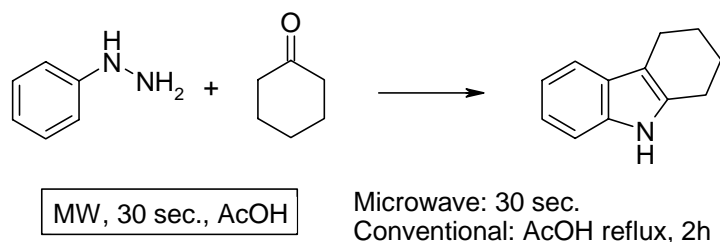The Hantzsch dihydropyridine synthesis remains one of the most important routes to pyridine ring systems. Under conventional conditions long periods of heating are required and yields are poor to moderate. Microwaves dramatically reduce the heating times and also significantly increase the yields as shown in Scheme 12.[14]
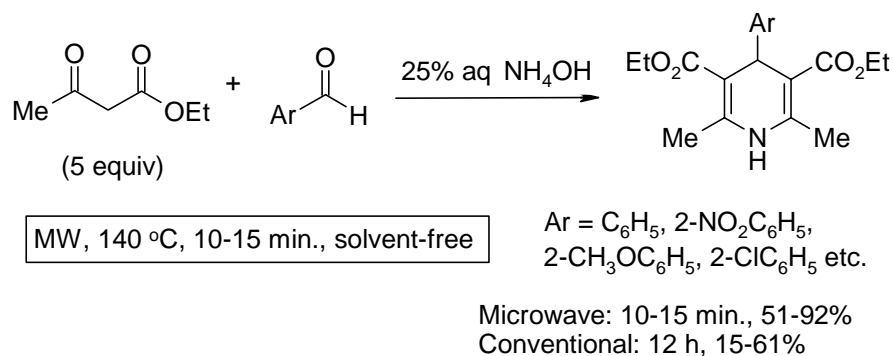
Scheme 12

1.3.2. Dihydropyridopyrimidinones

Dihydropyridopyrimidinones have been produced by ring annulations of aminopyrimidinones. Once again the reaction time is dramatically reduced and yields are much better with the solvent-free microwave conditions (Scheme 13).[15]

X = O, S; R = H, CH₃;
Ar = C₆H₅, 4-CH₃OC₆H₄,
4-ClC₆H₄

Microwave: 15-20 min., 70-75%
Conventional: EtOH reflux, 40-48 h, 21-25%
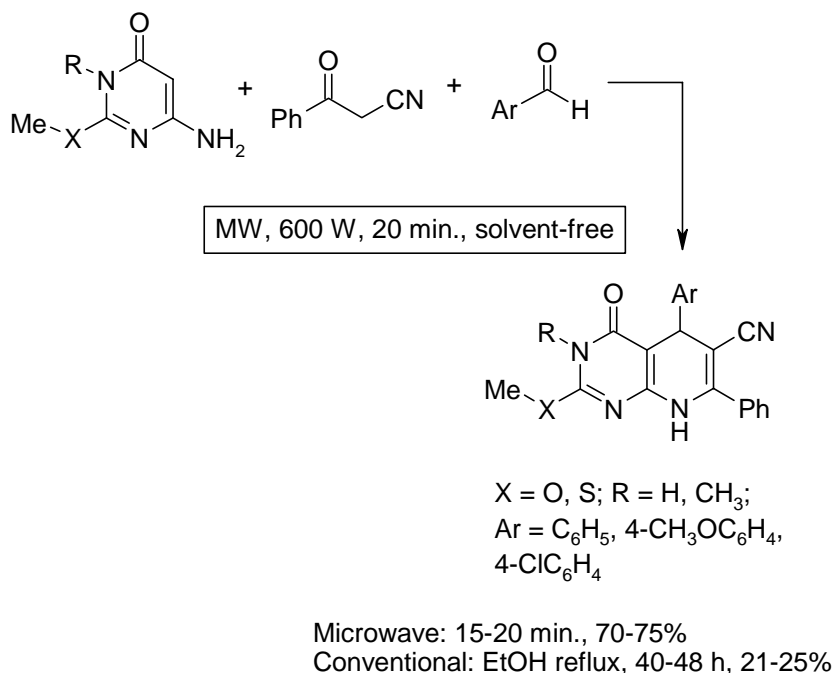
Scheme 13

1.3.3. Dihydropyrimidines

The Biginelli reaction is important for the preparation of dihydropyrimidine derivatives and excellent results are found for reactions carried out with microwave enhancement (Scheme 14).[3]

Microwave: 5 min., 60-90% yield
Conventional: 12-24 h, 15-60% yield
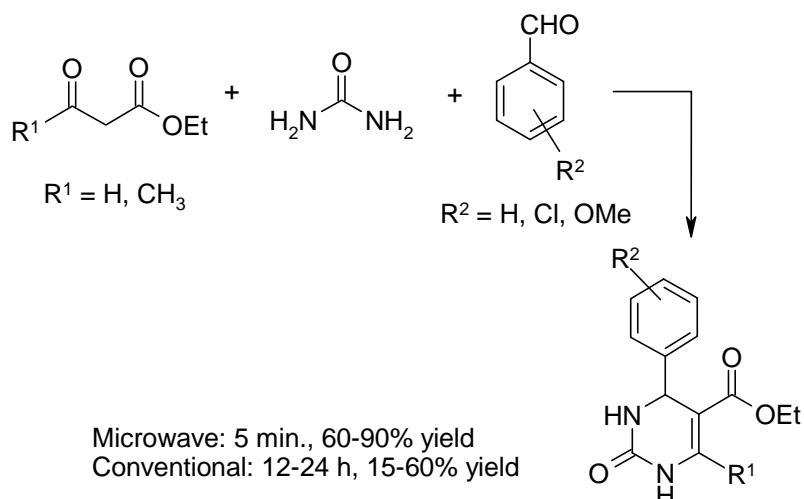
Scheme 14

1.3.4. Tetrazines

The Diels-Alder reaction between aza-olefins and aza-dicarboxylic ester to give tetrazines is speeded-up by a factor of 1000 by microwave enhancement as shown in Scheme 15.[16]

R = carbohydrate

MW, 300 W, solvent-free

80-96%

Microwave: 15 min.
Conventional: 30 days
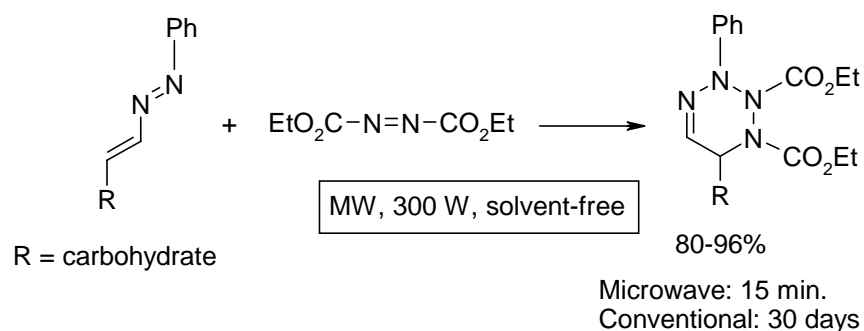
Scheme 15

1.4. Polycyclic six-membered rings
1.4.1. Quinolines

The Skraup synthesis has a bad reputation as it involves very messy conditions and gives only low yields of quinolines when carried out conventionally. Recently, it has been reported that microwave enhancement reduces the reaction time to a few minutes and allows high yields to be isolated (Scheme 16).[17]

R = H, *o*-CH$_3$, *m*-CH$_3$, *p*-CH$_3$,
    o-OMe, *p*-OMe, *m*-OH, *m*-Cl etc.
R^1 = H, CH$_3$, *n*-C$_3$H$_7$; R^2 = H, C$_2$H$_5$;
R^3 = CH$_3$, *p*-MeOC$_6$H$_4$

Microwave: 80-87%
Conventional: H$_2$SO$_4$/150 ^{o}C, low yields
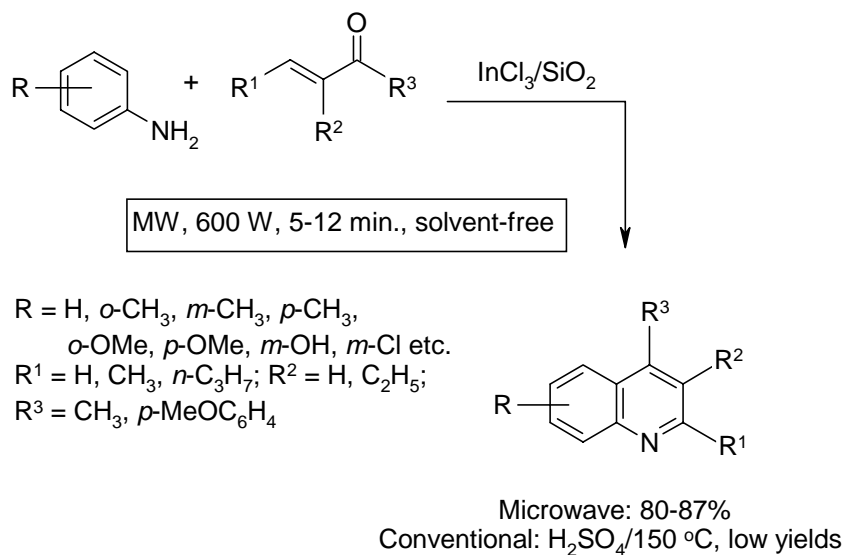
Scheme 16

1.4.2. Pyrimido[1,2-*a*]pyrimidines

Pyrimido[1,2-*a*]pyrimidines are prepared from dihydroaminopyrimidines and chromone-3-aldehydes as is shown in Scheme 17.[18] Although the conventional reaction must proceed in refluxing ethanol, reactions are much faster and better yields have been obtained with microwaves.

Ar = C$_6$H$_5$, 4-CH$_3$C$_6$H$_4$,
4-CH$_3$OC$_6$H$_4$, 4-ClC$_6$H$_4$,
2-thienyl

4H

2H

Microwave: 20 min., > 95%
Conventional: EtOH reflux, 4 h, 60-70%
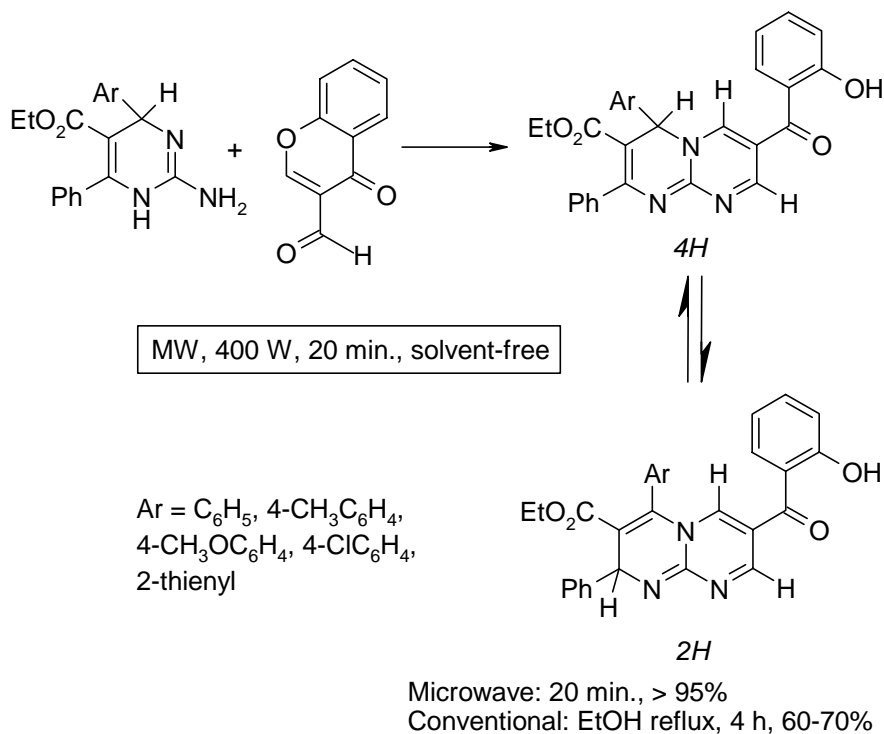
Scheme 17

Until now we have concentrated on reactions in which heterocyclic rings are formed. However, microwave assistance can also be extremely valuable in many other types of reactions in heterocyclic chemistry.

2. Nucleophilic Substitutions

2.1. Heterocyclic *C*-alkylations

Nucleophilic substitution reactions can be speeded-up very considerably as is illustrated in Scheme 18 for a chloro-naphthyridine derivative.[3]
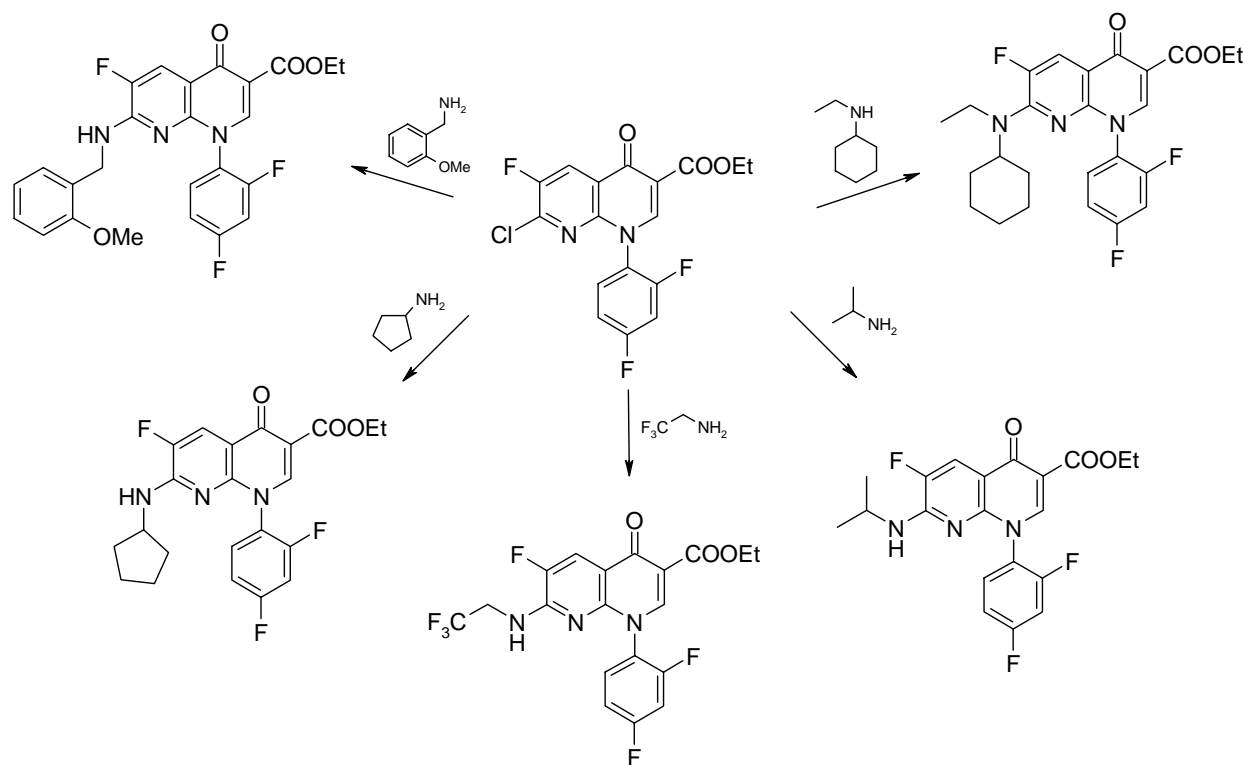
Microwave: 175 ºC, 10 min., 100%
Conventional: 100 ºC, 12-24 h, 35-60%

Scheme 18

2.2. Heterocyclic N-alkylations

Another class of nucleophilic substitution is involved in heterocyclic *N*-alkylation which we have illustrated in Scheme 19. This shows that nucleophilic substitution on the nitrogen atom of saccharin is significantly speeded-up by microwave irradiation.[19]

MW, 750 W, 2-10 min., solvent-free

71-92%

Microwave: 10 min.
Conventional: DMF reflux, 30 min.

$R = CH_2C_6H_5$,
$n\text{-}C_{16}H_{33}$,
$CH_2COOC_2H_5$ etc.

Scheme 19

2.3. Selective-alkylation

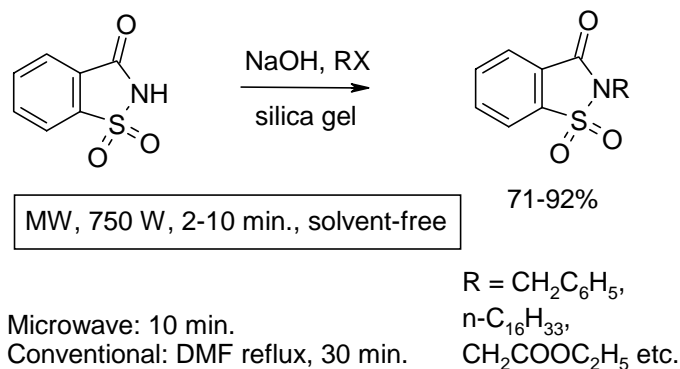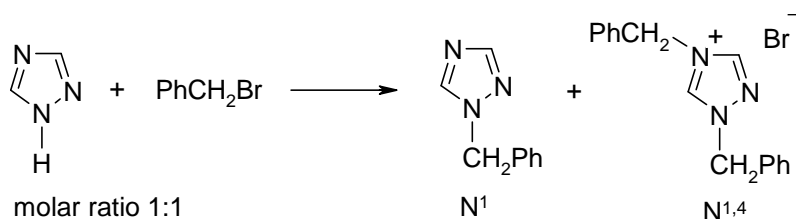In Scheme 20, the results presented indicate that selectivity is achieved in the *N*-alkylation of 1,2,4-triazole under microwave conditions where only the N^1-alkyl derivative was formed in contradistinction to the conventional conditions which give a considerable amount of the di-1,4-substituted compound.[20]

molar ratio 1:1 N^1 $N^{1,4}$

Microwave: 90-165 °C, 1.5-5 min., 70%; only N^1
Conventional: 14%; only $N^{1,4}$ isolated

Scheme 20

2.4. Transition metal cross-coupling

An important type of nucleophilic substitution reactions which are recently much exploited are comprised of transition metal cross-coupling. A Suzuki coupling is shown at the top of Scheme 21 to give significantly better yield in the presence of microwave irradiation.[21a] At the bottom of Scheme 21 another Suzuki coupling is speeded-up by a factor of 100.[21b]

MW, 160 W, 105 ºC, 12 min., H$_2$O   Microwave: 73%
                                       Conventional: 42%

Microwave: 30 sec.
Conventional: 48 h   60%
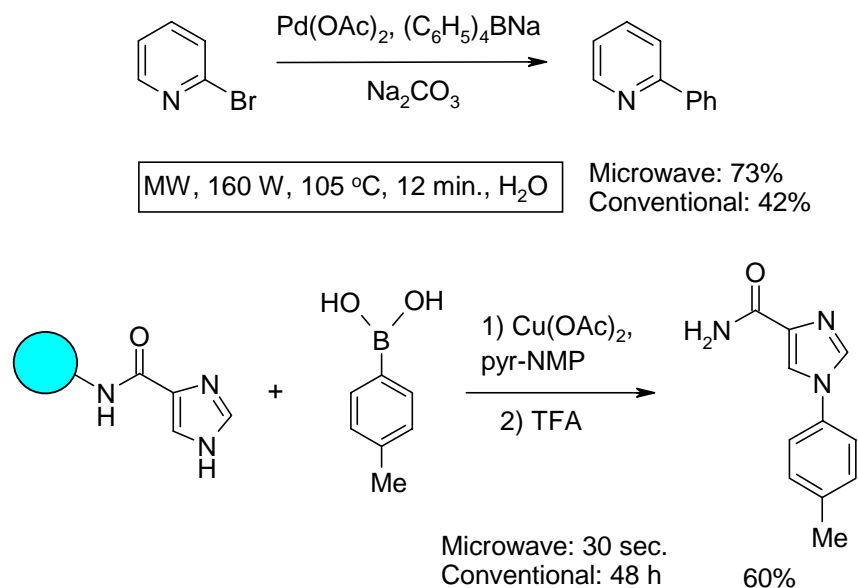
Scheme 21

3. Hetero-Diels−Alder reactions

3.1. Intramolecular reactions

We have already seen one example of a hetero-Diels−Alder reaction involving acyclic components. Hetero-Diels−Alder reactions involving cyclic components which lead to polycyclic ring systems are of great importance. An intramolecular example shown in Scheme 22 indicates that the reaction was accelerated by a factor of around 1000 by microwave irradiation.[22]

MW, 300 W, 190 ºC, 8-15 min., DCE, bmimPF$_6$

MW, 300 W, 130 ºC, 5 min.

+ H$_2$O

57-77%

Microwave: 13-20 min.
Conventional: PhCl reflux, 2-3 days   R = Bn, Ph; n = 2, 3
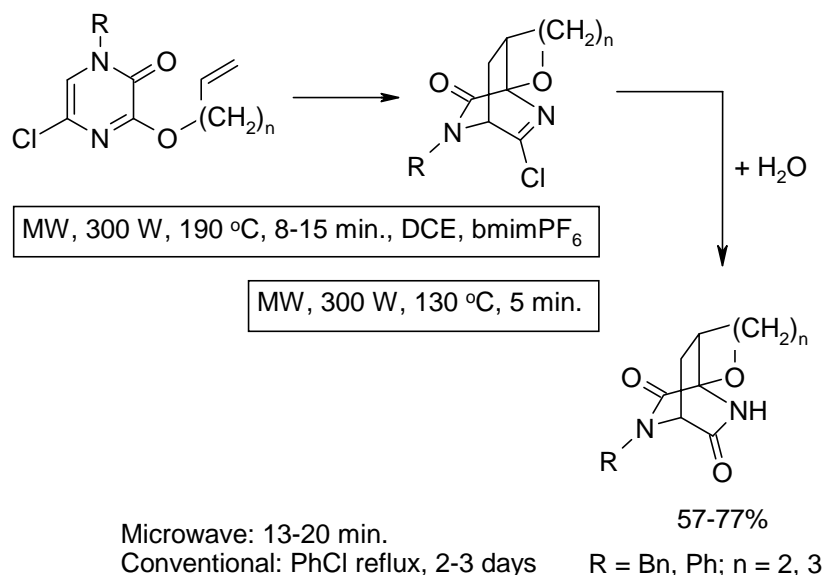
Scheme 22

3.2. Intermolecular reactions

Scheme 23 shows two impressive examples of rate enhancement for intermolecular hetero-Diels−Alder reactions.[22] In the first example on the top of Scheme 23 the initial reaction is followed by elimination thus involving the conversion of a pyrazine derivative into a pyridine. Perhaps more impressive is the lower example in Scheme 23 where an autoclave is required under conventional conditions but which can be dispensed with when microwave acceleration is utilized.
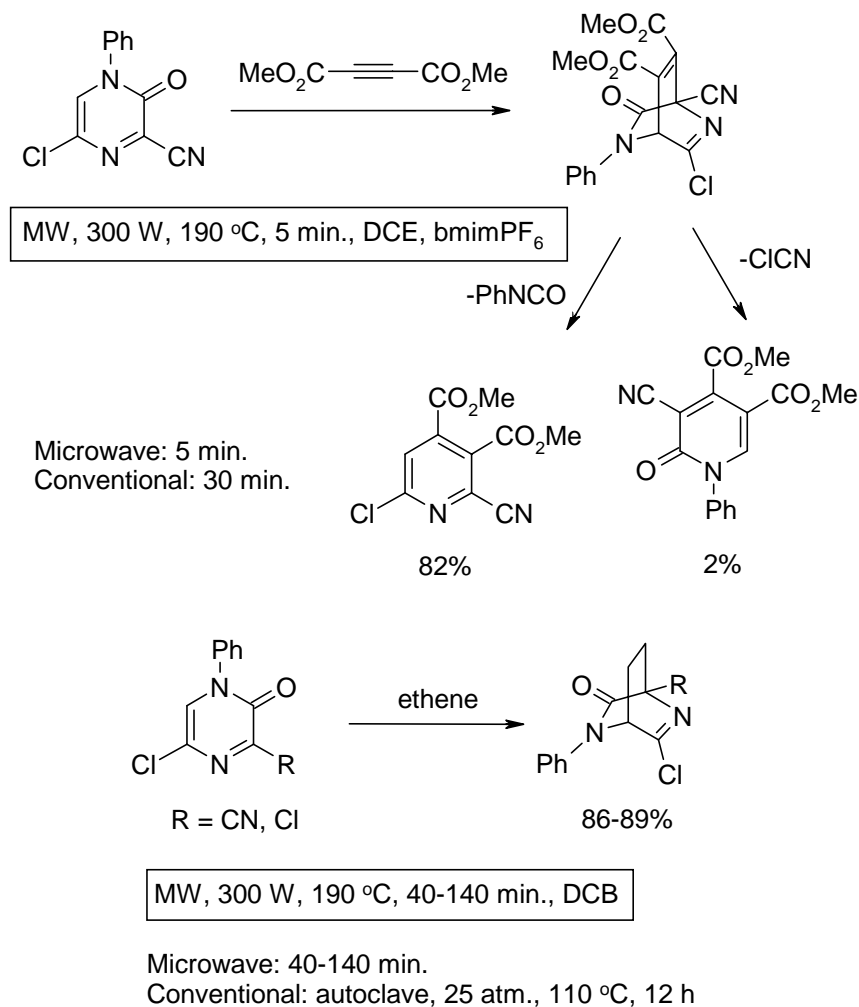
Scheme 23

4. 1,3-Dipolar cycloaddition reactions

4.1. Synthesis of *C*-carbamoyl-1,2,3-triazoles

We now turn to some of our own recent work which has involved microwave induced 1,3-dipolar cycloaddition of organic azides to acetylenic amides. As shown in Scheme 24 we were able to achieve these reactions under microwave conditions in a reasonable time at temperatures of around $70\pm15\ ^{\circ}C$.[23] Under conventional conditions the times were roughly 100 times as long and the temperature had to be taken up to $120\ ^{\circ}C$.[24]
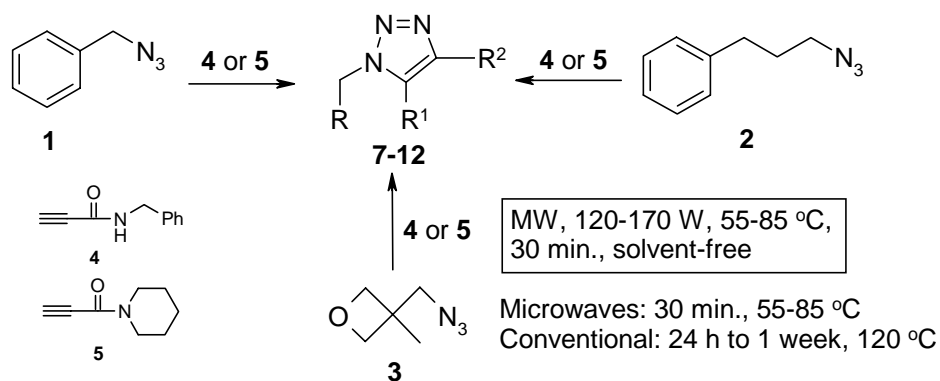
	R	R^1	R^2	Y(%)^a
7	Ph	H	CONHCH$_2$Ph	65
8	Ph	H	COpiperidinyl	63
9	Ph(CH$_2$)$_2$	H	CONHCH$_2$Ph	62
10	Ph(CH$_2$)$_2$	H	COpiperidinyl	65
11	C(CH$_3$)(CH$_2$OCH$_2$)	H	CONHCH$_2$Ph	84
12	C(CH$_3$)(CH$_2$OCH$_2$)	H	COpiperidinyl	80

^{a}Isolated yield of major regioisomer.

Scheme 24

4.2. Synthesis of substituted mono-triazoles

Scheme 25 shows some similar results of rate enhancements of formation of mono-triazoles from alkoxycarbonyl-activated acetylenes and azides.[25]
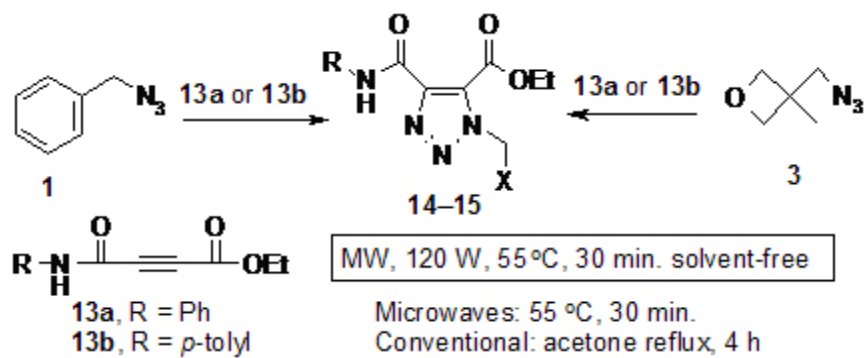
	R	X	Y(%)^a
14a	Ph	Ph	83
14b	p-tolyl	Ph	84
15a	Ph	C(CH$_3$)(CH$_2$OCH$_2$)	72
15b	p-tolyl	C(CH$_3$)(CH$_2$OCH$_2$)	63

^{a}Isolated yield of major regioisomer.

Scheme 25

4.3. Synthesis of substituted bis-triazoles

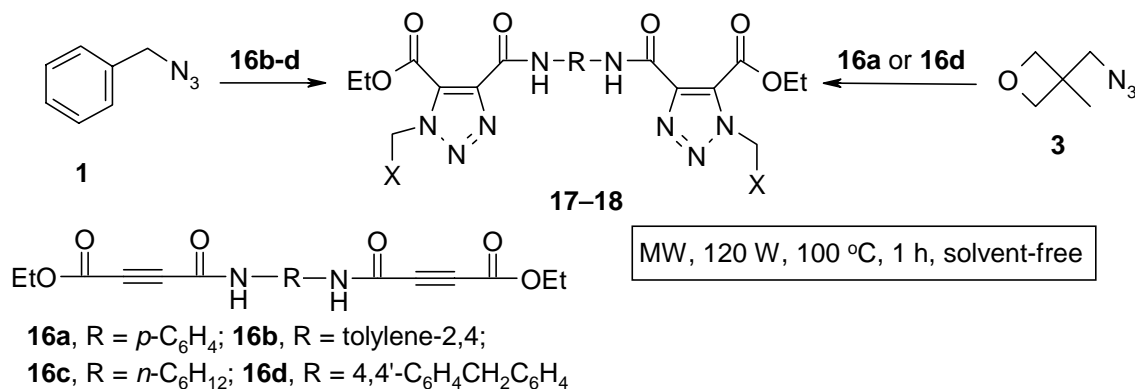In Scheme 26 examples are shown of the preparation of bis-triazoles from mono-azides and bis-amidopropiolates. In Scheme 27 we were able to make bis-triazoles from di-azide and mono-amidopropiolates.[25] This should be appropriate for the preparation of polymers utilizing bis-triazoles and bis-amidopropiolates.

16a, R = p-C$_6$H$_4$; **16b**, R = tolylene-2,4;
16c, R = n-C$_6$H$_{12}$; **16d**, R = 4,4'-C$_6$H$_4$CH$_2$C$_6$H$_4$

	R	X	Y(%)[a]
17b	tolylene-2,4	Ph	41
17c	n-C$_6$H$_{12}$	Ph	37
17d	4,4'-C$_6$H$_4$CH$_2$C$_6$H$_4$	Ph	73
18a	p-C$_6$H$_4$	C(CH$_3$)(CH$_2$OCH$_2$)	43
18d	4,4'-C$_6$H$_4$CH$_2$C$_6$H$_4$	C(CH$_3$)(CH$_2$OCH$_2$)	42

[a]Isolated yield of major regioisomer.

Scheme 26

MW, 120 W, 75 ºC, external cooling, 1 h, toluene
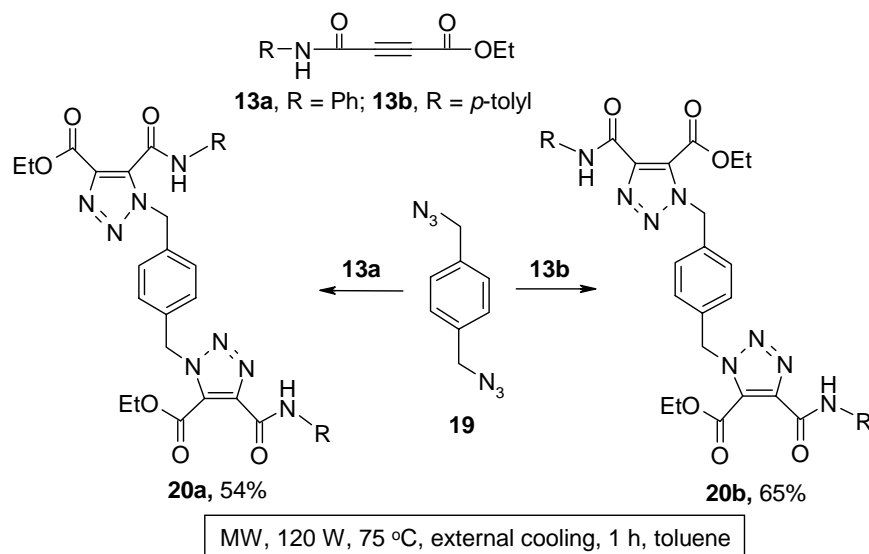
Scheme 27

5. *N*-Chlorination of amides
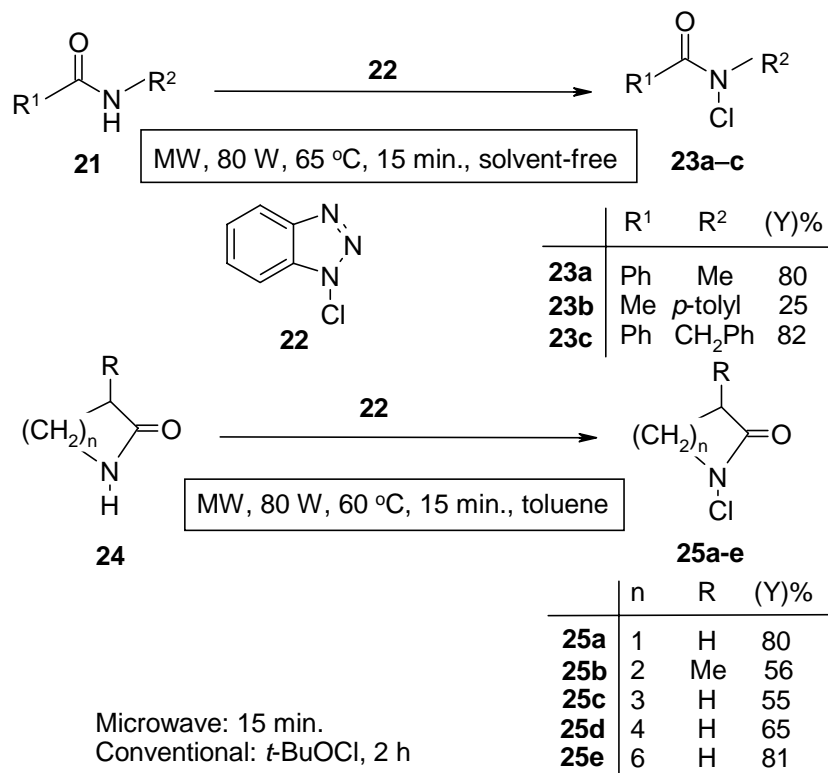
Very recently, we have been able to show that *N*-chlorination can be carried out under very mild conditions and in high yields utilizing 1-chlorobenzotriazole (Scheme 28).[25] Conventional methods for *N*-chlorination generally involve reaction with *tert*-butyl hypochlorite in methanol for 2 h.[26]

	R^1	R^2	(Y)%
23a	Ph	Me	80
23b	Me	*p*-tolyl	25
23c	Ph	CH_2Ph	82

	n	R	(Y)%
25a	1	H	80
25b	2	Me	56
25c	3	H	55
25d	4	H	65
25e	6	H	81

Microwave: 15 min.
Conventional: *t*-BuOCl, 2 h

Scheme 28

In conclusion, we have summarized the recent applications of microwave activation in the synthesis and reactions of heterocycles. In comparison to conventional methods, microwave heating offers advantages such as reduced reaction times and temperatures, better yields, selectivity and reproducibility especially due to the advent of single-mode technology.

Acknowledgments

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