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Microwave-assisted Domino Reaction in Organic Synthesis

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1. Introduction

The fields of combinatorial and automated medicinal chemistry have emerged to meet the increasing requirement of new compounds for drug discovery, where speed is of the essence (Loupy, 2002). In this regard, domino (or tandem, or cascade) reactions where "two or more bond-forming transformations take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step" are especially suitable for the generation of libraries of bioactive small molecules (Tietze, 1996, 2000, 2006; Domling, 2006). When performed intermolecularly, they are used to couple small fragments to larger units. In intramolecular reactions, they can bring about cyclizations or bicyclizations, and thus astonishing changes of molecular structures and increases in molecular complexity. This effect can even be enhanced by repeating the same reaction type several times or combining it with a different transformation in a domino fashion. Such sequential processes offer a wide range of possibilities for the efficient construction of high structural diversity and molecular complexity in the desired scaffolds in a single synthetic step simply by proper variation of precursors, thus avoiding time-consuming and costly processes for purification of various precursors and tedious steps of protection and deprotection of functional groups (de Meijere et al., 2005; Tietze et al., 2009). Additionally, they frequently occur with enhanced regio-, diastereo-, and even enantioselectivity for the overall transformation (Ikeda, 2000; Domling & Ugi, 2000; D'Souza & Mueller, 2007).

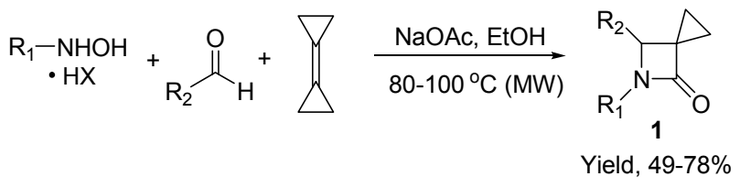
Simultaneously, the emergence of sustainable microwave chemistry has further impacted synthetic chemistry significantly since the introduction of precision controlled microwave reactors. From the pioneering experiments of Gedye (Gedye et al., 1986) and Giguere (Giguere et al., 1986), the use of microwave irradiation as an energy-efficient heat source for accelerating chemical reactions including heterocycle-forming, condensation, and cycloaddition reactions has seen widespread application (Kappe, 2000; Kappe & Stadler, 2005, 2009; Loupy, 2006; Kappe et al., 2009). Therefore, the high density microwave irradiation has matured into a reliable and useful methodology for accelerating reaction processes for the collection of heterocycles. Not only is direct microwave heating able to reduce chemical reaction times from hours to minutes and seconds, but it is also known to reduce side reactions, increase yields, and improve reproducibility. As a result, many academic and industrial research groups are already using microwave-assisted organic

synthesis (MAOS) as a forefront technology for rapid optimization of reactions, for the efficient synthesis of new chemical entities, and for discovering and probing new chemical reactivity. Thus, it has become clear that the combined approach of microwave superheating as an energy-efficient heat source with domino reaction, in particular those carried out using precision-controlled microwave reactors, offers an efficient synergistic strategy, which can be rapidly introduced or broadened structural diversity in heterocyclic chemistry. In this chapter, we have summarized our recent activity in the area of microwave chemistry for domino synthesis of bioactive small molecules.

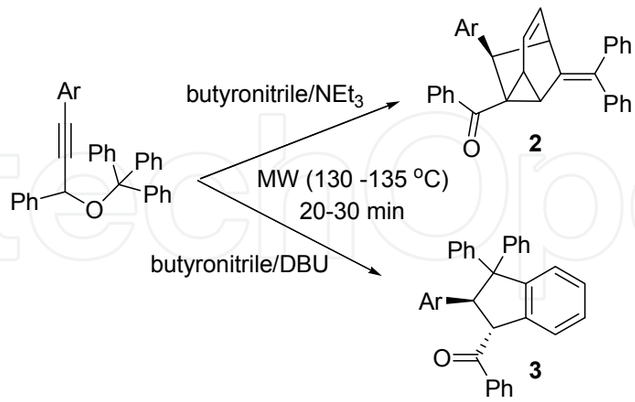
2. MW-assisted domino cyclization

2.1 The construction of four-, five-membered ring

A three-component domino reaction of certain alkylhydroxylamine hydrochlorides (alkyl = benzyl, p-methoxybenzyl, benzhydryl, tert-butyl) with formaldehyde or an alkyl glyoxylate and bicyclopropylidene to furnish 3-spirocyclopropanated 2-azetidinones **1** has been described by Meijere and co-workers (Eq. 1) (Zanobini et al., 2006). Microwave heating of mixtures of the three components in the presence of sodium acetate in ethanol for 15–120 min furnished the β-lactams **1** in 49%–78% yield. In any case, the reaction time required under microwave heating is less than 2 h, whereas with traditional heating at 45 °C the 1,3-dipolar cycloaddition of the most reactive N-methyl-C-(ethoxycarbonyl)nitrone onto bicyclopropylidene requires 16 d, and only spirocyclopropanated piperidones was generated when the reaction was performed at higher.



(1)

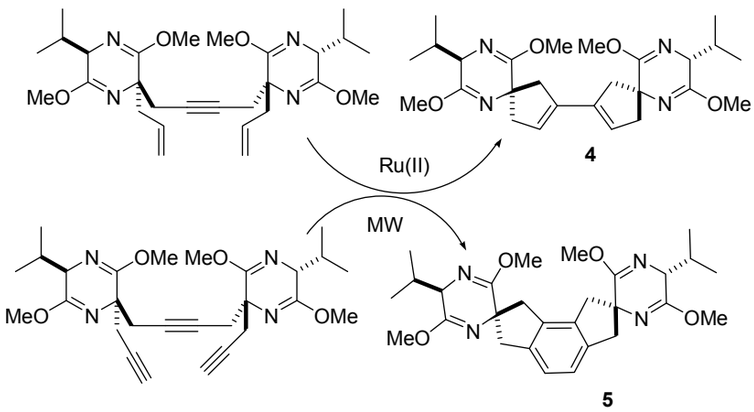


(2)

Microwave-assisted unimolecular isomerizatio-Claisen domino reactions of 1,3-di(hetero)aryl propargyl trityl ethers selectively lead to the formation of tricyclo[3.2.1.$0^{2,7}$]oct-3-enes **2** depennding on the basicity of the amine (Eq. 2) (D'Souza et al., 2008). When triethylamine was as a base, the reaction generated structurally complex tricyclo[3.2.1.$0^{2,7}$]oct-3-enes in 82%-93% yield, but limited scope of this reaction, whereas the reaction gave indanes **3** in 62%-94% yields using DBU as a base at 100-130 °C for 5-20 min.

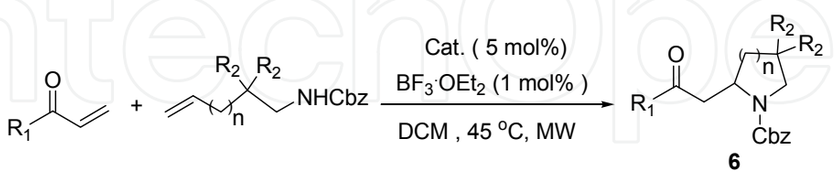
Based upon product analyses and computations, this base dependent dichotomy can be rationalized as a sequel of pericyclic reactions with intermediate protonation and deprotonation.

The high temperature microwave-accelerated ruthenium-catalysed domino ring-closing metathesis (RCM) reactions for the construction of a bicyclic and a tricyclic annulated ring system were described (Efskind & Undheim, 2003). The direct conversion of the dienyne to bicyclic annulated product **4** in the presence of standard Grubbs' catalyst $(PCy_3)_2Cl_2Ru{=}CHPh$ was observed in 76% yield by microwave heating in toluene at 160 °C for 45 min. For comparison, in the conventional preparative work very little RCM product was obtained, even after prolonged reaction times. Under the same reaction condition, triyne was highly converted to tricyclic annulated compound **5** in 100% yield for 10 min (Eq. 3).



(3)

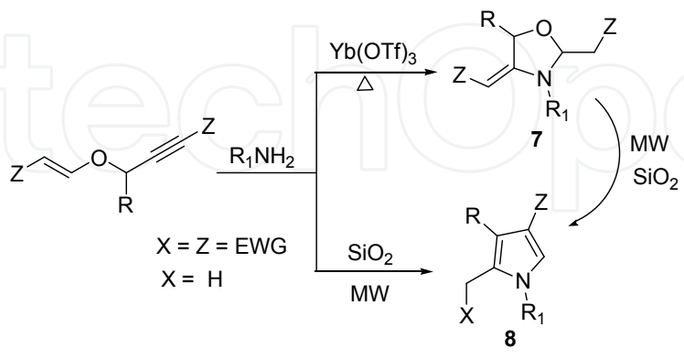
The cyclic β-amino carbonyl derivatives **6** were synthesized via microwave-assisted tandem cross metathesis intramolecular aza-Michael reaction between vinyl ketone and amine (Fustero et al., 2007). During the optimization process, the best result was obtained in dichloromethane in the presence of Hoveyda-Grubbs catalyst using $BF_3{\cdot}OEt_2$ as additive at 100 °C for 20 min (Eq. 4). The same reaction was performed under conventional heating at 45 °C for 4 days. Under optimized condition, a series of cyclic β-amino carbonyl derivatives were yielded. The domino process is independent of the ketone substitution affording good to excellent chemical yields in the formation of both five- and six-membered rings.



(4)

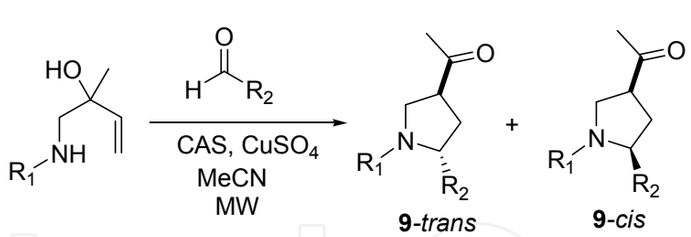
A new microwave-assisted rearrangement of 1,3-oxazolidines scaffolds **7** is the basis for a metal-free, direct, and modular construction of tetrasubstituted pyrroles **8** from terminal-conjugated alkynes, aldehydes, and primary amines (Tejedor et al., 2004). The synthetic protocol embodyed two coupled domino processes in a one-pot manner with both atom- and bond-efficiency and under very simple and environment-friendly experimental conditions. Microwave-assisted rearrangement of 1,3-oxazolidines absorbed on silica gel for 5 min cleanly afforded the 1,2,3,4-tetrasubstituted pyrrole derivative **8** with good yield (Eq. 5). The conjugated alkynoate (1 mmol) and the amine (1.3 mmol) were absorbed on 1 g of

silica gel and irradiated at 900 W for 8 min to the corresponding 1,2,3,4-tetrasubstituted pyrroles in 38%-77% yields. The process is general for the amine and tolerates a range of functionalities in the aldehyde. The authors proposed plausible mechanism for this new MW-assisted rearrangement of 1,3-oxazolidines and further investigated reaction mechanism.



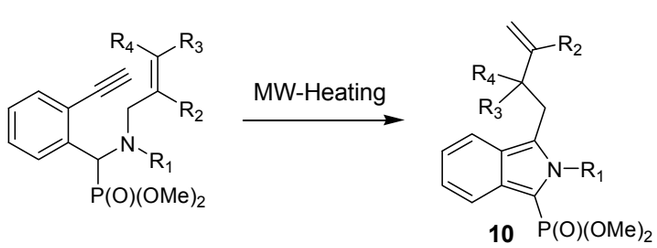
(5)

The group of Lindsay reported the synthesis of the acylpyrrolidines (**9-***trans* and **9-***cis*) *via* the tandem aza-Cope rearrangement–Mannich cyclization between the amino alcohol and aldehydes with varied functionalities (Eq. 6) (Johnson et al., 2007). Under microwave heating the reaction proceed smoothly at 60-90 °C for 5-150 min to provide the acylpyrrolidines **9** with 22%-84% yields. Performing the reactions at lower temperatures led to the higher observed diastereoselectivities in some cases. This sequence provides in a single synthetic step while significantly reducing reaction times as compared to analogous reactions using conventional heating.



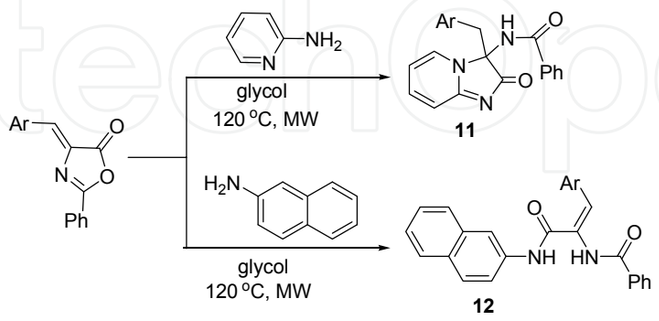
(6)

The high-temperature rearrangement cyclization of *o*-ethynylbenzyl-aminophosphonates to yield isoindoles **10** was achieved by microwave heating in a 1:1 mixture of benzene/CH_3CN (Dieltiens & Stevens, 2007). A set of structurally complex isoindoles **10** were generated in 40%-98% yield at 165 °C for 60-180 min under microwave heating (Eq. 7). The reaction mechanism was proposed including addition, [1,3]-alkyl shift and aromatization based on [1,5]-H shift.



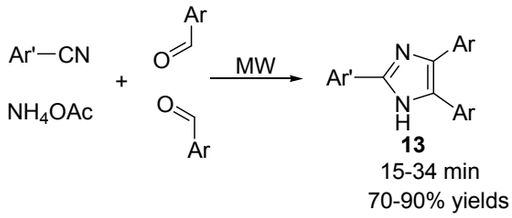
(7)

The group of Tu developed the cascade reaction of 4-(arylmethylene)-2-phenyloxazol-5(4*H*)-one with pyridin-2-amine to generate 13 new imidazo[1,2-*a*]pyridin-2-one derivatives **11** in 62%-78% yield in ethylene glycol at 120 °C under microwave irradiation (Eq. 8) (Tu et al., 2007, a). The aromatic amine, instead of pyridin-2-amine, reacted with 4-(arylmethylene)-2-phenyloxazol-5(4*H*)-one to give open-ring prop-2-enamides **12** with good yield (82%-90%). The starting materials were easily obtained and the operation was convenient.



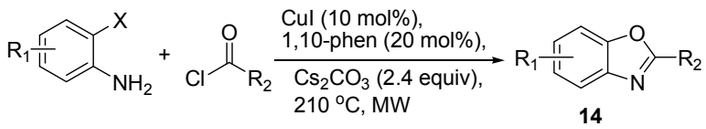
(8)

Recently, Tu and Li's groups established a concise and efficient four-component domino approach to highly substituted 2-(2'-azaaryl)imidazoles **13** under solvent-free and microwave-irradiation conditions (Jiang et al., 2009, a). The four-component reaction offers several advantages including broad scope of substrates where a wide range of common commercial aromatic aldehydes and heteroaryl nitriles can be used with shorter reaction times (15-34 min). The desired products were obtained in good to excellent chemical yields without the tedious workup isolations. A new mechanism involving an umpolung has been proposed for this reaction (Eq. 9).



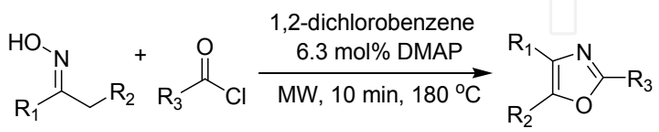
(9)

The sequential domino annulation approaches for benzoxazole synthesis have been reported by the group of Batey (Viirre et al., 2008). Benzoxazoles **14** were formed in good yields for the reaction of 1,2-dibromobenzene, but the reaction has no regioselectivity using 3,4-dibromotoluene as inputs. Furthermore, the method is limited by the availability of 1,2-dihaloarenes. As a result of these limitations, an alternative more versatile one-pot domino annulation strategy was described involving reaction of 2-bromoanilines with acyl chlorides in the presence of Cs_2CO_3, catalytic CuI, and the non-acylatable ligand 1,10-phenanthroline. Under these conditions initial acylation of the aniline is followed by copper-catalyzed intramolecular cyclization of the resultant 2-haloanilide to form the Ar-O bond of the benzoxazole ring. Optimized conditions using microwave irradiation achieved much shorter reaction times (15 min) than conventional heating (24 h) and were applied to the synthesis of a small library of benzoxazoles in 21%-97% yields. These copper-catalyzed approaches using 2-haloanilines compliments existing approaches to benzoxazoles that instead rely upon the use of 2-aminophenols (Eq. 10).



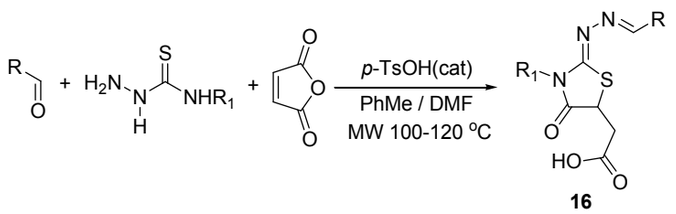
14 (10)

Microwave irradiation promotes the rapid O,N-acylation–cyclodehydration cascade reaction of oximes and acid chlorides to give oxazoles **15 (**Eq. 11) (Wipf et al., 2005). The microwave irradiation allowed considerable acceleration of the rate of oxazole formation and increased the yield of this synthetically attractive heterocycle formation process. The starting oximes were readily obtained from commercially available ketones in yields exceeding 90%, and the yields of isolated oxazoles ranged from 23% to 62%.

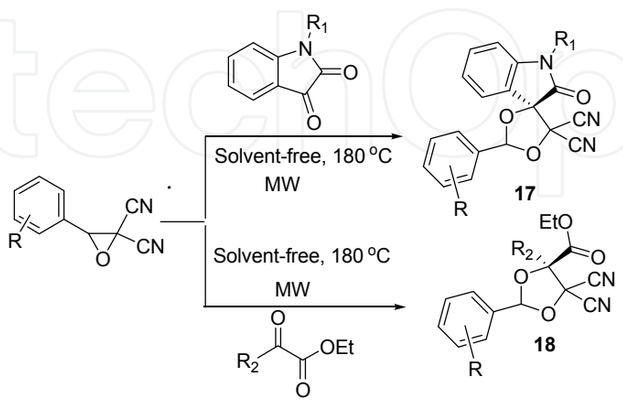


15 (11)

A tandem method for the synthesis of 2-hydrazolyl-4-thiazolidinones **16** from commercially available materials in a 3-component reaction was reported by the Mahler group(Eq. 12) (Saiz et al., 2009). The reaction connects aldehydes, thiosemicarbazides, and maleic anhydride, effectively assisted by microwave irradiation. The best yields were obtained using a co-solvent mixture of PhMe/DMF (1:1) at 120 °C. Under optimized microwave conditions, a range of aromatic and some aliphatic aldehydes were converted to the desired heterocycles. Aromatic aldehydes provided good yields from 45% to 82%, at 120 °C for 6–12 min reaction time, except for 2-thiophene-carboxaldehyde.



16 (12)

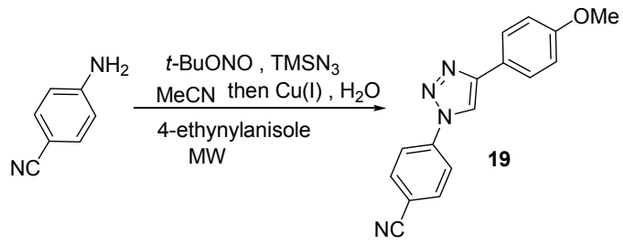


17 18 (13)

Mongin and co-workers presented the [3+2] cycloaddition reaction between carbonyl ylides generated from epoxides and ketones (α-ketone ester and isatin derivatives) to give substituted spirocyclic dioxolane indolinones **17** and dioxolanes **18** with a low

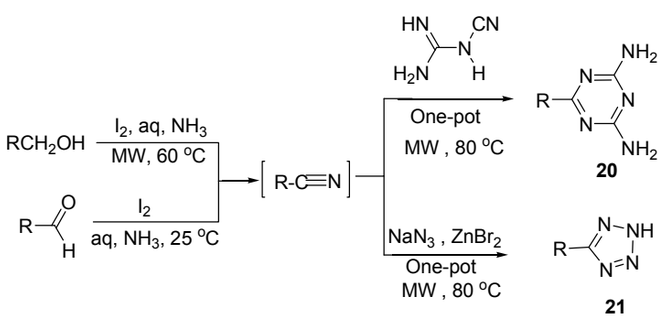
stereoselectivity and a large regio- and chemoselectivity (Eq. 13) (Bentabed-Ababsa et al., 2008). This reaction is a domino process that comprises two steps: the first is the thermal ring opening of the epoxide to yield a carbonyl ylide intermediate, whereas the second step is a polar [3+2] cycloaddition to provide the final spiro cycloadducts. The more favorable channels are associated with the nucleophilic attack of the isatin carbonyl oxygen atom to the phenyl substituted carbon atom of the carbonyl ylide. Using microwave irradiation significantly reduced reaction times (30-55 min) in comparison to reaction in toluene at reflux (14-29 h).

Moses and co-workers reported a modification of the methodology, using microwave radiation to significantly enhance the rate of formation of a variety of 1,4-triazole products **19** with good to excellent yield (80%-99%) from a selection of readily available anilines and acetylenes (Moorhouse & Moses, 2008). The procedure is particularly amenable to electron-deficient anilines, and works well with a wide variety of alkynes including aromatic, conjugated, aliphatic, electron-rich and electron-deficient varieties. The practical and efficient one-pot azidation of anilines with the reagent combination *t*-BuONO and $TMSN_3$ has become a useful addition to the click-chemistry toolbox. The products were rapidly isolated by precipitation and filtration directly from the reaction mixture with no further purification (Eq. 14).



(14)

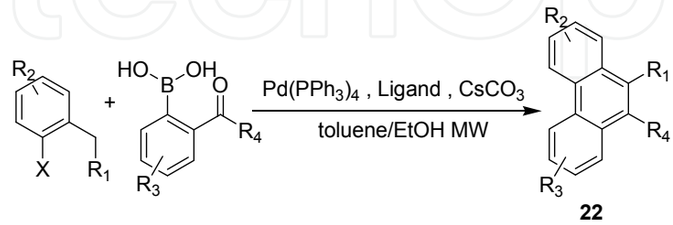
The Fang group described the direct conversion of an aldehyde with iodine in ammonia water to a nitrile intermediate, which without isolation was heated with dicyandiamide, using microwave heating at 80 °C, to furnish the [2+3] cycloaddition product 2,6-diamino-1,3,5-triazine **20** in a one-pot operation (Shie & Fang, 2007). The reaction time was shortened to 15-30 min. The aldehydes were subjected to oxidation with I_2 in ammonia water and in situ cycloadditions with $NaN_3/ZnBr_2$ by microwave irradiation at 80 °C for 10 min to give the 5-aryl-1,2,3,4-tetrazoles **21** in 70%-83% overall yields. In comparison with the conventional heating method using prolonged reflux (17-48 h) at a high temperature (>100 °C), the microwave-accelerated reaction in aqueous media is safer and more efficient (Eq. 15).



(15)

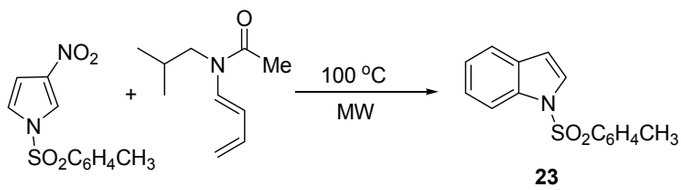
2.2 The construction of six- and seven-membered ring

Heo's group presented a one-pot cascade reaction of Suzuki-Miyaura coupling/aldol condensation as an efficient method for the construction of phenanthrene derivatives **22** (Kim et al., 2008). Coupling of aryl bromide with lboronic acid in the presence of a Pd catalyst and Cs_2CO_3 provided phenanthrenes **22** with 56%-90% yield using co-solvent of toluene and ethanol (v/v:1:4) under microwave heating. Also, the cascade reaction of pinacol boronate ester with 2-bromobenzaldehyde under the same conditions afforded the phenanthrene **22** in slightly lower yield (56%-71% yield) than that of aryl bromide with boronic acid (Eq. 16).



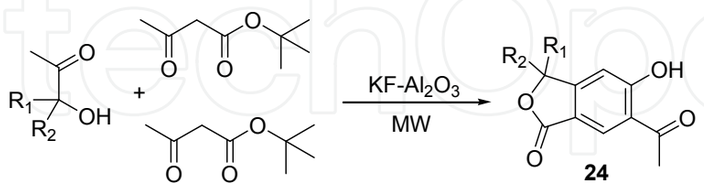
22 (16)

Moreno and co-workers showed that under microwave irradiation the cycloaddition reactions of nitropyrroles in solvent-free conditions give 27%-71% yields of the aromatic indoles **23**, through elimination of the nitro group and subsequent aromatization (Eq. 17) (Victoria Gomez et al., 2009).



23 (17)

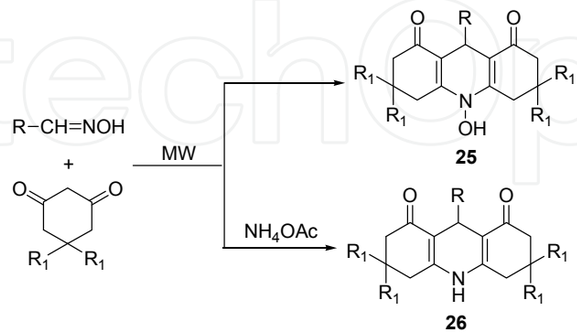
The reaction of α-hydroxyketones with a double equivalent of *t*-butyl acetylacetonate in the presence of KF-alumina under microwave irradiation afforded isobenzofuran-1(3*H*)-ones **24** in moderate yield (42%-53%) (Villemin et al., 2006). This work involving one-pot three-component cascade process is significant, although only four products were synthesized (Eq. 18).



24 (18)

Tu's group reported the synthesis of the *N*-hydroxylacridine derivatives **25** in 83%-91% yields through reaction of the substituted aryl aldeoxime with dimedone in glycol under microwave irradiation for 4-7 min (Eq. 19) (Tu et al., 2004). When ammonium acetate was added to this reaction system under the same conditions, the good to excellent yields of acridine derivatives **26** were obtained. In addition, these reactions could not take place when ketoximes were employed as starting materials. The same authors presented another highly efficient synthesis of a series of new pyrido[2,3-*d*]pyrimidine-4,7-dione derivatives **27** and **28** via a novel cascade reaction of 4-arylidene-3-methylisoxazol-5(4*H*)-ones (or 4-arylidene-2-

phenyl-5(4*H*)-oxazolones) with 2,6-diaminopyrimidin-4(3*H*)-one, or naphthalen-2-amine,respectively (Tu et al., 2007, b). The microwave-assisted reaction conditions was optimized, and co-solvent of DMF and HOAc (V/V = 2:1) as reaction media at 140 °C gave best results. 31 desired pyrido[2,3-*d*]pyrimidine-4,7-dione derivatives with high diastereoselectivity were synthesized in 76%-91% yield (Eq. 20). This method has the advantages of shorter reaction time and convenient operation.



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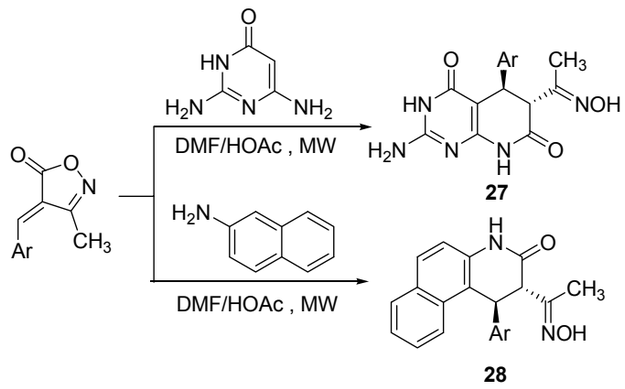
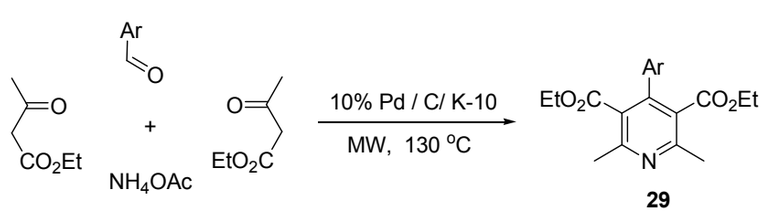


(20)

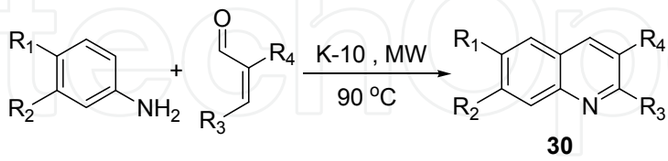
The group of Torok reported one-pot synthesis of substituted pyridines **29** via a domino cyclization–oxidative aromatization (dehydrogenation) approach (De Paolis et al., 2008). The process is based on the use of a new bifunctional Pd/C/K-10 montmorillonite and microwave irradiation. The reaction of aromatic aldehydes with ethyl acetoacetate and ammonium acetate proceeded to give a set of 4-aryl substituted pyridines **28** in good to excellent yields (45%-95%) at 130 °C. Also, the aliphatic aldehydes were converted to the corresponding substituted pyridines in high yields (Eq. 21).The microwave-assisted process appears to be widely applicable and affords the products in good to excellent yields, high selectivities and in short reaction times compared to traditional heating.



(21)

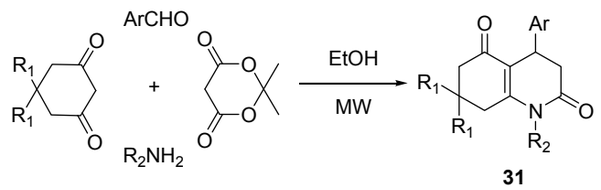
The same author described a microwave-assisted montmorillonite K-10-catalyzed synthesis of quinolines **30** from anilines and cinnamaldehydes (Eq. 22) (Torok et al., 2009). The

cyclization and oxidation steps readily take place in a domino approach. The reaction works well at 90 °C under free-solvent condition to give the substituted quinolines in 55%-95% yields, completed in a matter of minutes. As compared to conventional heating, microwave irradiation benefit significantly in regard to more efficient reaction time, yield and product purity. The efficient and ecofriendly catalyst and the convenience of the product isolation make this process an attractive alternative for the synthesis of these important heterocycles.



30 (22)

Tu's group reported a concise four-component reaction of aldehydes, Meldrum's acid, dimedone, and different amines in 95% ethanol without catalyst under microwave conditions, and a series of new *N*-substituted 4-aryl-tetrahydroquinoline-2,5-dione derivatives **31** with 82%-95% yields were afforded (Eq. 23) (Tu et al., 2006). The experimental results showed that structurally diverse aldehydes including electron-drawing, electron-donating, and hetero-aromatic aldehydes were tolerated in the reaction. It is also observed that the protocol can be applied to different amines (including aliphatic and alicyclic amines) but also to aromatic amines which highlight the wide scope of this four-component condensation.



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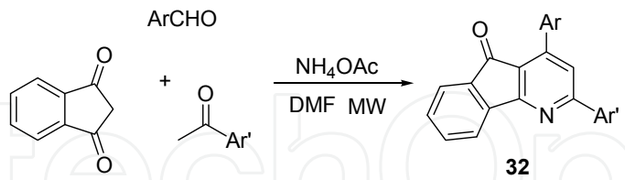
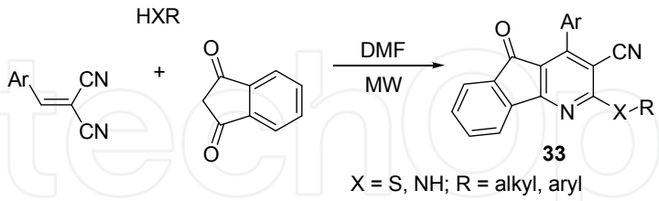


32 (24)

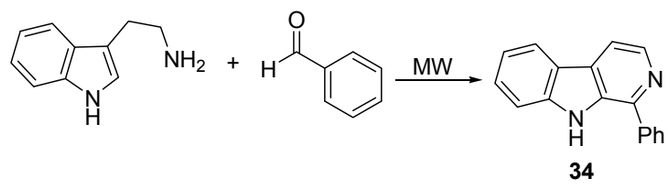
In next work, four-component domino condensation for the synthesis of indenopyridine derivatives **32** has been described (Eq. 24) (Tu et al., 2007, c). Investigation of reaction condition was found to be *N*,*N*-dimethylformamide (DMF) and 120 °C under microwave heating. Structurally diverse arone substrates were employed to react with different aldehydes and 1,3-indanedione in the present of ammonium acetate, providing the corresponding indeno[1,2-*b*]pyridin-5-ones in 62%–89% yields. The 2-(pyridin-2-yl)-indeno[1,2-*b*]pyridines was first synthesized in the MCRs. To realize green synthesis of 2-(pyridin-2-yl)-indeno[1,2-*b*]pyridines with important property, the same reaction were preformed using water as solvent in a sealed vial under microwave heating at 150 °C (Tu et al., 2007, d). To broaden the diversity of indeno[1,2-*b*]pyridines, Tu's group developed a new domino three-component reaction of arylidenemalononitrile with 1,3-indanedione and

mercaptoacetic acid (or 4-methylbenzenethiol, or aromatic amine) under microwave (MW) irradiation to afford 27 libraries of indeno[1,2-*b*]pyridines **33** with good to excellent yields (78%-91%) (Eq. 25) (Tu et al., 2007, e). The best reaction condition was found to be in DMF at 120 °C for 4-12 min.



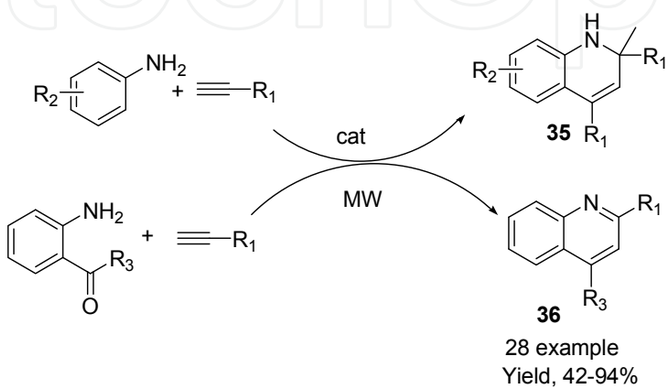
(25)

Huang and Torok reported rapid, microwave-assisted synthesis of *β*-carbolines **33** via a successive condensation / cyclization / dehydrogenation approach (Eq. 26) (Kulkarni et al., 2009). The use of the bifunctional catalyst Pd/C/K-10 combined with microwave irradiation enabled the synthesis of β-carbolines in short reaction times and in good to excellent yields. The reactions between tryptamine and aromatic glyoxals provide excellent yield (79%-96%) in 2–12 min, whereas tryptamine reacted with aromatic aldehydes give similar yield (71%-90%), demanding longer reaction time (20-45 min). The product imine undergoes a Pictet–Spengler cyclization followed by a final dehydrogenation to yield *β*-carbolines in a three-step domino reaction.



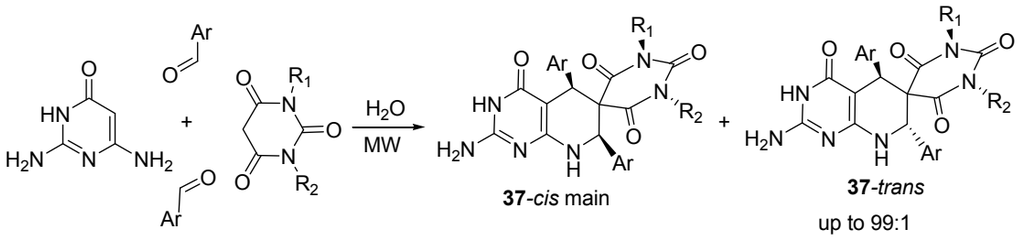
(26)

A method to efficiently prepare substituted 1,2-dihydroquinolines **35** and quinolines **36** by Au(I)-catalyzed tandem hydroamination-hydroarylation under microwave irradiation was developed (Eq. 27) (Liu et al., 2007). The best result was obtained when the reaction of primary arylamines with alkynes at 150 °C in the presence of additive NH_4PF_6 using Au(I) /AgOTf as catalysts with CH_3CN as solvent, and a set of quinoline derivatives **34** and **35** were obtained in 42-94% yields. This method requires short reaction time 10-70 min and has a broad substrate scope.

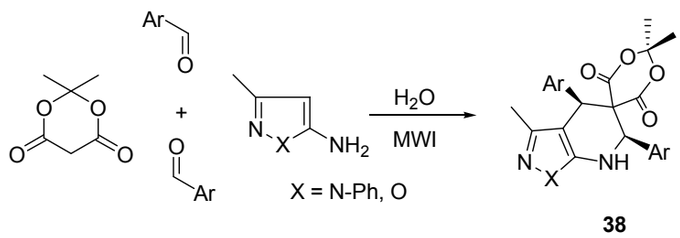


(26)

The Tu's group reported a new and highly stereoselective four-component protocol for the domino reactions of 2,6-diaminopyrimidine-4-one with structurally diverse aryl aldehydes and various barbituric acids, resulting in 19 examples of 6-spirosubstituted pyrido[2,3-*d*]pyrimidines **37** with high diastereoselectivities (up to 99 : 1) in which the major diastereomer bears a *cis* relationship between substituents at the 5- and 7-positions (Eq. 28) (Jiang et al., 2009, b). These reactions employ microwave heating and water as an environmentally benign reaction medium at 100 °C for 7-9 min. Furthermore, the mechanism for diastereoselectivity was confirmed by DFT (B3LYP) calculations. Subsqently, new multicomponent domino reactions of Meldrum's acid, aromatic aldehydes and electron-rich heteroaryl-amines have been established for the synthesis of spiro{pyrazolo[1,3]dioxanes-pyridine}-4,6-diones and spiro{isoxazolo [1,3]dioxanes-pyridine}-4,6-diones **38** in aqueous solution under microwave irradiation (Eq. 29) (Ma et al., 2010). A total of 26 examples were examined to show a broad substrate scope and high overall yields (76%-93%). A new mechanism has been proposed to explain the reaction process and the resulting chemo-, regio- and stereoselectivity.

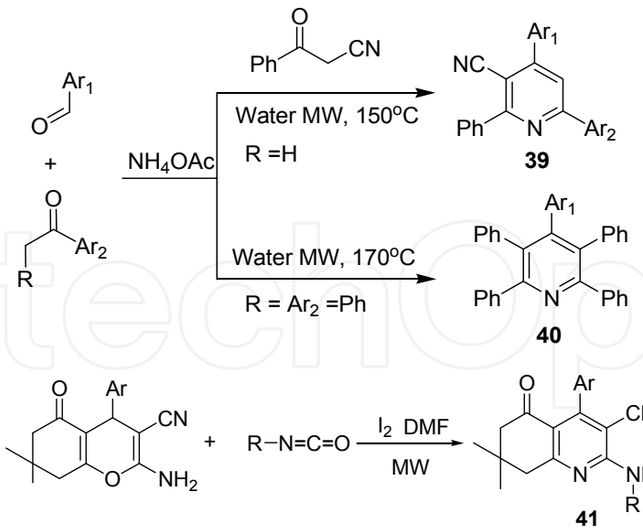


(28)



(29)

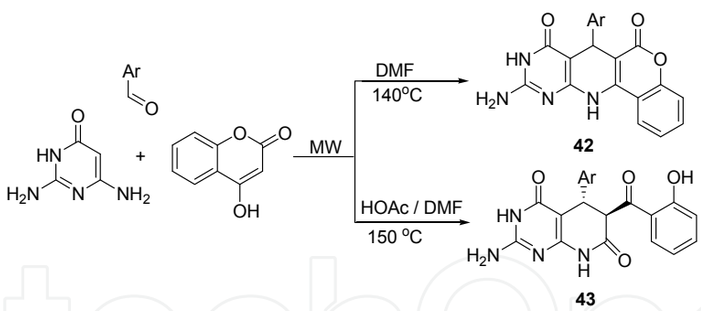
Recently, Tu's group described an efficient reagent-controlled regiospecific synthesis of 2,2'-bipyridine and unsymmetrical 2,4,6-triarylpyridine derivatives **39** at high-temperature via microwave-assisted aqueous multicomponent domino reactions of aromatic aldehydes, 3-aryl-3-oxopropanenitrile, 2-acetylpyridine or aromatic ketone and ammonium acetate (Jiang et al., 2009, c). The reaction of aromatic aldehydes with 1,2-diphenylethanone resulted in structurally complex penta-arylpyridines **40**. This serves as an efficient general approach to diversity-oriented poly aryl pyridine skeletons (Eq. 30). Later on, the same group reported a new iodine-promoted domino reaction of 2-aminochromene-3-carbonitriles with various isocyanates, and 19 examples of polyfunctionalized *N*-substituted 2-aminoquinoline-3-carbonitriles with high regioselectivity were successfully synthesized under microwave heating (Jiang et al., 2010). The syntheses were finished within short periods (20-36 min) with good to excellent chemical yields (62%-85%) that avoided tedious work-up isolations (Eq. 31).



(30)

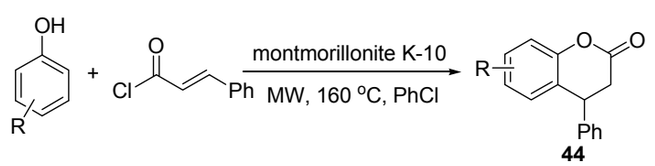
(31)

The same group also developed the multicomponent reaction of arylaldehyde, 4-hydroxy-2*H*-chromen-2-one and 2,6-diaminopyrimidin-4(3*H*)-one for the construction of pyrido[2,3-*d*]pyrimidine and chromeno[3′,4′:5,6]pyrido[2,3-*d*]pyrimidine skeletons **42** and **43** containing a pyridine unit controlled by the nature of solvent (Eq. 32) (Tu et al., 2008). The 9 examples of polysubstituted chromeno[3′,4′:5,6]pyrido[2,3-*d*]pyrimidines **42** in 83%-90% yields was generated using DMF as a solvent, whereas the reaction was found to undergo along another pathway leading to the formation of pyrido[2,3-*d*]pyrimidines **43** in 82%-92% chemical yields when the reaction was conducted in mixed solvent of HOAc and DMF.



(32)

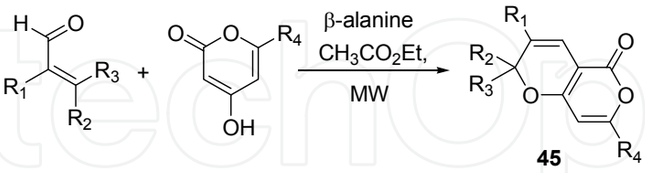
Ma and co-workers presented the synthesis of dihydrocoumarin derivatives **44** through the reaction between phenols and cinnamoyl chloride using montmorillonite K-10 as eco-friendly solid-acid catalyst via a tandem esterification–Friedel–Crafts alkylation process under microwave irradiation (Zhang et al., 2008). 10 examples with 25%-92% yield were generated at 160 °C in chlorobenzene (Eq. 33).



(33)

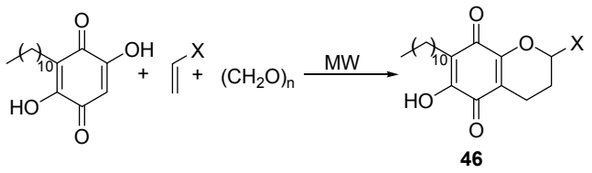
Beifuss et al. described a domino process for the preparation of libraries of substituted pyrano[4,3-*b*]pyran derivatives **45** in a single step by reaction of an α,β-unsaturated aldehyde

with 6-substituted-pyran-2-one (Eq. 34) (Leutbecher et al., 2004). Microwave-assisted reaction was run at 110 °C in the presence of calcium sulphate to give the heterocycles 3 with 18%-88% yields for 10-90 min. Even if the yields obtained are still lower than under conventional condition, the reactions under microwave heating condition benefit from considerable time savings and a substantially more rapid access to pyrano[4,3-*b*]pyran collections.



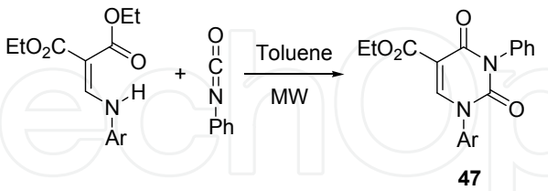
(34)

Estevez-Brau & Ravelo described the synthesis of novel pyrano embelin derivatives **46** through domino Knoevenagel hetero Diels–Alder reactions of embelin with paraformaldehyde and electron rich alkenes (Eq. 35) (Jimenez-Alonso et al., 2008). The author found that this synthetic approach is highly efficient when microwave irradiation is used, and the EtOH as a solvent at 120 °C for 20 min gave the best result using the ratio of embelin, ethyl vinyl ether and paraformaldehyde in 1:3:8. A et of dihydropyran–embelin derivatives with good to excellent yield (50%-100%) were obtained employing several dienophiles.



(35)

Jimenez and co-workers introduced a new domino strategy, involving the coupling of enaminoesters with chlorosulfonyl isocyanate enables the straightforward preparation of the biologically important isoorotate bases **47** with moderate to good yields (Eq. 36) (Avalos et al., 2006). As compared to the refluxing in toluene within 48 h, the reaction was completed for 1 h under microwave irradiation.



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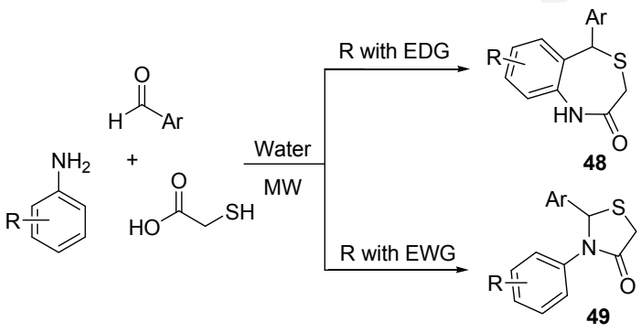
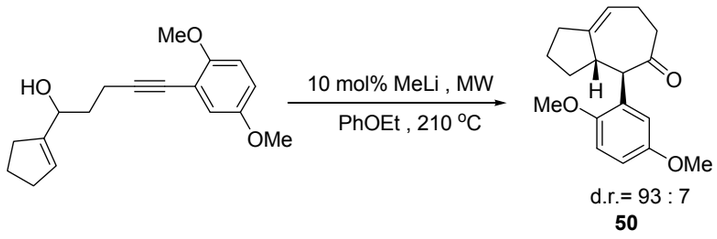


(37)

The group of Tu described a highly efficient and chemoselective synthetic route to the benzothiazepinones **48** and thiazolidinones **49** *via* a microwave-assisted three-component reaction of an aromatic aldehyde with aniline and mercaptoacetic acid (Eq. 37) (Tu et al., 2009). The reaction gave best results in water at 110 °C, and 25 benzothiazepinones were synthesized in 90%-96% yield under the optimum reaction conditions. The influences of electronic effect on the chemoselectivity were investigated in these reactions. The aromatic aldehydes bearing electron-donating groups (EDG) as well as heteroaromatic aldehydes resulted in benzothiazepinones whereas electron-withdrawing groups (EDG) on phenyl ring generated thiazolidinones **49.** When 3,4-(methylenedioxy)aniline was used as the inputs, aromatic aldehydes bearing both electron-withdrawing and electron-donating groups led to the benzothiazepinones **48** in all the case.

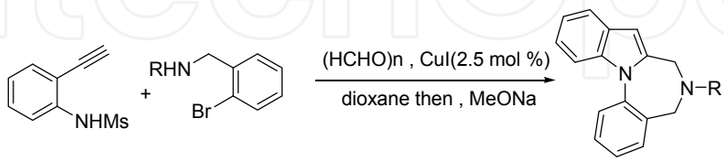
A number of substituted cyclohept-4-enone derivatives **50** in 45%-89% yield were synthesized via a microwave-assisted tandem oxyanionic 5-exo cyclization/Claisen rearrangement sequence using appropriately substituted 1-alkenyl-4-pentyn-1-ol systems served as useful precursors (Eq. 38) (Li, et al., 2007). All reactions were conducted at 210 °C for 45 or 60 min in the presence of 10 mol % MeLi and using phenetole as the solvent and microwave heating. The reactions involving terminally substituted 4-pentyn-1-ols were found to be highly stereoselective (up to 93:7), with the α and β groups in the final product showing a strong preference for the *trans* orientation.



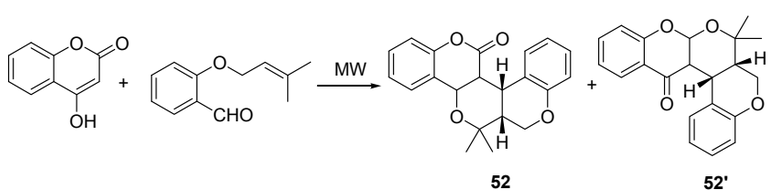
(38)

2.3 The construction of bicyclic ring

Indole-fused benzo-1,4-diazepines **51** were synthesized by copper-catalyzed domino three-component coupling-indole formation-*N*-arylation under microwave irradiation from a simple *N*-mesyl-2-ethynylaniline (Eq. 39) (Ohta et al., 2008). Investigation of the reaction solvent and loading of the catalyst revealed that 2.5 mol% of CuI in dioxane most effectively produced **51** in 88% yield within 40 min. this method was also applicable to the formation of heterocycle-fused 1,4-diazepines.

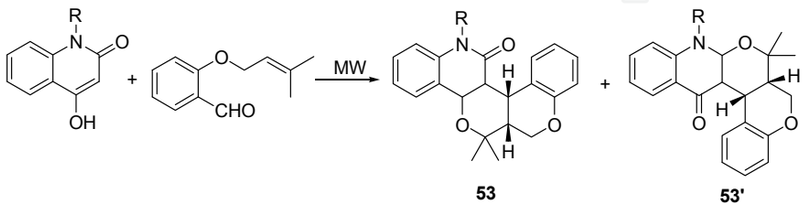


(39)



(40)

The group of Raghunathan described 4-hydroxy coumarin and its benzo-analogues undergo intramolecular domino Knoevenagel heter Diels-Alder reactions with *O*-prenylated aromatic aldehydes, the aliphatic aldehydes, and citronellal to afford pyrano[3-2*c*]coumarin derivatives **52** and **52′** (Eq. 40) (Shanmugasundaram et al., 2002, a). Compared with conventional condition (yield, 40%-75%), the higher yield (74%-92%) and chemoselectivity (up to 95: 5) of products were achieved by the application of microwave irradiation within a short period of time (10-180 s). The same authors reported the similar versions to pyranoquinolinone **53** and **53′** (Eq. 41) (Jayashankaran et al., 2002), thiopyrano coumarin/chromone **54** and **54′** (Eq. 42) (Raghunathan et al., 2006), and pyrrolo[2,3-*d*]pyrimidine annulated pyrano[5,6-*c*]coumarin/[6,5-*c*]chromone derivatives **55** and **55′** (Eq. 43) (Ramesh & Raghunathan, 2008) under microwave heating.



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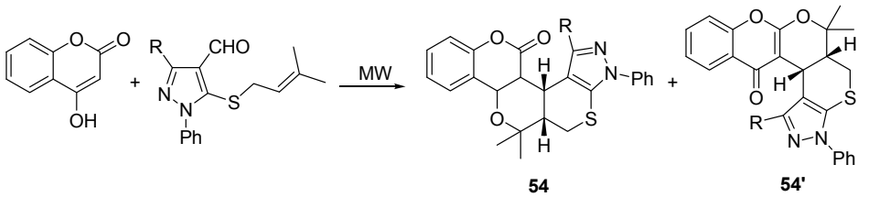
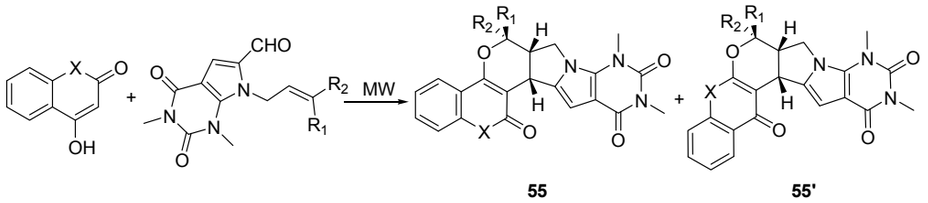
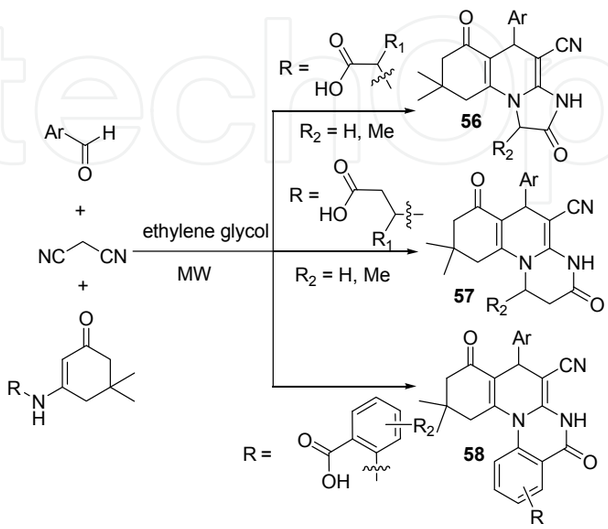


(42)

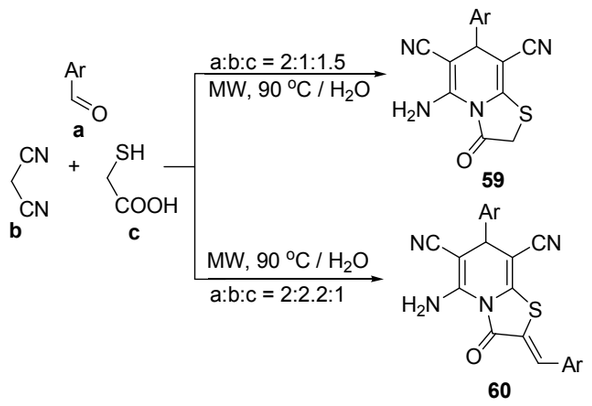


(43)



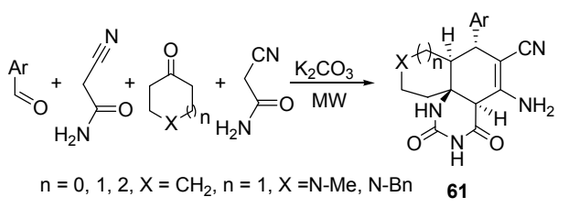
(44)

The group of Tu developed a high-speed and one-pot combinatorial strategy for the diverse quinoline collections, including imidazo[1,2-*a*]quinoline **56**, pyrimido[1,2-*a*]quinoline **57**, and quinolino[1,2-*a*]quinazoline **58** moiety, from readily available starting materials (Eq. 40) (Tu et al., 2007, f). The best yields (80%-89%) of products were obtained in ethylene glycol at 120 ^{o}C for 4-8 min. The authors combined the advantages of microwave heating with combinatorial chemistry to facilitate the rapid construction of biheterocyclic system such as imidazo[1,2-*a*]quinoline, pyrimido[1,2-*a*]-quinoline, and quinolino[1,2-*a*]quinazoline keletons, and 42 desired products were synthesized via multicomponent reaction of aromatic aldehyde, malononitrile, and *N*-substituted enaminones. The green chemoselective synthesis of thiazolo[3,2-*a*]pyridine derivatives **59** and **60** was achieved by the same group recently (Eq. 45) (Shi et al., 2009). The MCR of malononitrile, aromatic aldehydes and 2-mercaptoacetic acid was preformed to produce two different products by controlling the molar ratios of the starting materials. These products have been screened for their antioxidant activity and cytotoxicity in carcinoma HCT-116 cells and mice lymphocytes. Nearly all of the tested compounds possessed potent antioxidant activity.



(45)

The group of Tu and Li recently discovered a new four-component domino reaction between simple aldehydes, cycloketones and cyanoamides, and a diverse set of quinazoline derivatives **61** in 74%-90% yields were obtained, with the remarkable chemo-, regio- and stereoselectivity (Eq. 46) (Jiang et al., 2009, d). The reaction is easy to perform simply by mixing four common reactants and K_2CO_3 in ethylene glycol under microwave irradiation. The reaction is very fast and can be finished within 10-24 min with water as the major byproduct, which makes work-up convenient. Four stereogenic centers with one quaternary carbon-amino function have been controlled very well. Later on, the same group found that when aromatic aldehydes were replaced by their aliphatic counterparts, the quinazoline derivatives were not generated. Interestingly, the reaction resulted in the formation of multi-functionalized tricyclo[6.2.2.0^{1,6}] dodecanes **62**. (Eq. 47) (Jiang et al., 2010).



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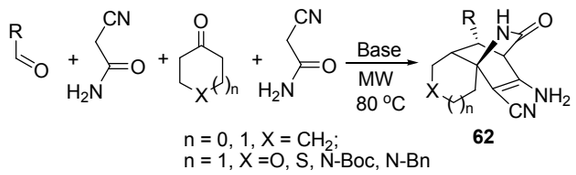
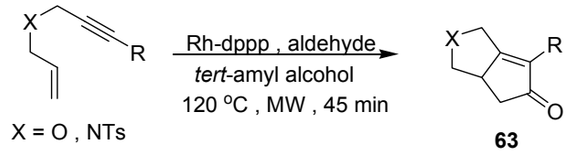


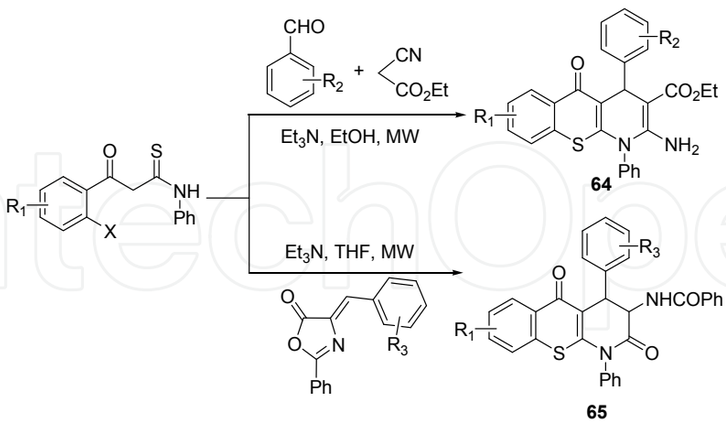
(47)

Kwong et al. reported microwave-assisted Rh–diphosphane-complex-catalyzed [2+2+1] cycloadducts to provide cyclopentenones **63** by sequential decarbonylation of aldehyde or formate and carbonylation of enynes within a short period of time (45 min) (Eq. 48) (Lee et al., 2008). Various O-, N-, and C-tethered enynes were transformed into the corresponding products in 34%-83% yields. The author also realized the enantioselective version of this microwave-accelerated cascade cyclization, and obtained the cyclopentenone products with *ee* values up to 90% in the presence of chiral Rh-(*S*)-bisbenzodioxanPhos complex.

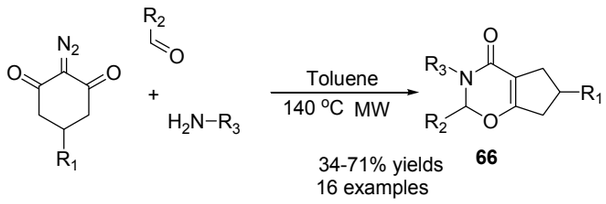


(48)

Li and co-workers synthesized a set of fused tricyclic thiochromeno[2,3-*b*]pyridines by tandem [3+3] annulation and SNAr reaction (Wen et al., 2008). Under microwave irradiation, *α*-(2-chloroaryl)thioacetanilides reacted with activated 4-arylidene-2-phenyloxazol-5(4*H*)-ones to give a small library of 24 thiochromeno[2,3-*b*]pyridines **64** with 54%-85% yield in THF catalyzed by triethylamine; whereas the three-component reactions of *α*-(2-chloroaryl)thioacetanilides and aromatic aldehydes with ethyl 2-cyanoacetate resulted in the corresponding thiochromeno[2,3-*b*]pyridine derivatives **65** with 52%-76% yield in EtOH (Eq. 49). In the domino processes, at least seven reactive distinct chemical sites were involved and up to three new covalent bonds and one tricycle with only *cis* configuration were generated.



(49)



(50)

The microwave-assisted Wolff rearrangement of cyclic 2-diazo-1,3-diketones in the presence of aldehydes and primary amines was described by the Coquerel and Rodriguez et al. (Eq. 50) (Presset et al., 2009). The reaction provides a straightforward access to functionalized bi- and pentacyclic oxazinones **66** following an unprecedented three-component domino reaction. The above approach to 1,3-oxazin-4-ones is the first example of the exploitation of the Wolff rearrangement in a multicomponent reaction.

3. Conclusion

In conclusion, microwave-assisted domino reactions have quickly become a powerful and efficient tool in organic chemistry. The combination of different activation modes allows the design of innovative domino sequences to afford high molecular complexity (Enders et al., 2007). In addition to the bond-forming economy (multiple formations of carbon-carbon or -heteroatom bonds), the microwave-assisted domino reaction intrinsically has the following advantages: the rapid optimization of procedures, high reaction selectivity and efficiency, consecutive reaction pattern, structure economy (structural complexity), and environmentally benign. Therefore, the combination of microwave heating and domino reaction opens numerous options for devising new sustainable synthetic methodologies in organic chemistry that are diversity oriented and increase complexity of molecular scaffolds. Recent advances have witnessed many new microwave-assisted domino reaction being developed, and provided more convenient and rapid procedures for heterocycles synthesis. The further extension to domino processed and the combination of three and more steps for introduction of small bioactive molecules libraries is still an interesting field in the very near future.

4. References

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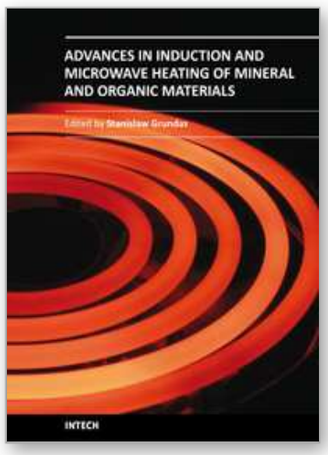

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