More Sustainable Approaches for the Synthesis of N-Based Heterocycles[†,‡]

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[‡] Dedicated to the memory of team member Jorge A. S. D. Pereira (1974−2009).
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1. Introduction

The use of energy and natural resources in the modern society for our living style is a very active subject for governments and the public sector. This pressure pursues

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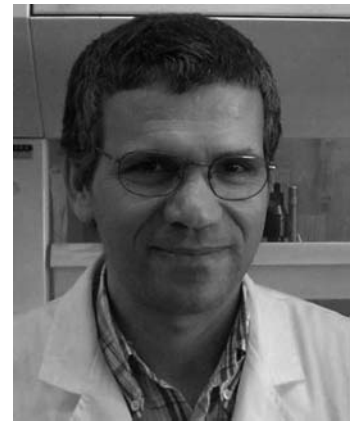
Nuno R. Candeias was born in Lisbon (Portugal) in 1981. He graduated in Applied Chemistry from New University of Lisbon (2004) and started his Ph.D. in chemistry titled "Intramolecular C-H Insertion of α-Diazoacetamides in Water" under the supervision of Professor Carlos A. M. Afonso at Technical University of Lisbon (2005−2008). He is currently working as a postdoctoral research fellow at the Pharmacy Faculty of the Lisbon University under the supervision of Dr. Pedro M. P. Góis and Professor Carlos F. Barbas III. His current interests are the development of synthetic methodologies and sustainable chemistry.

Luis Branco was born in Lisbon (Portugal). He obtained his degree in Chemistry (1998) at the Faculty of Sciences, University of Lisbon. In 1999, he started a research project in the Institute of Chemical and Biology, Oeiras (Portugal), working on "Synthesis of Hexaaza and Pentaaza Macrocyles" (under the supervision of Prof. Rita Delgado). In 2000, he moved to the Faculty of Science and Technology, New University of Lisbon. Then, he received an European Research Grant supported by European Project titled "New Remediation Technology for Vaccine Production Effluents Containing Organomercurials". In 2002, he started his Ph.D. at the Faculty of Science and Technology, New University of Lisbon, about "Development of New Ionic Liquids and their synthetic applications", under the supervision of Prof. Carlos Afonso. From June 2006 to March 2008, he worked as a postdoctoral research fellow at Department of Chemistry, University of Cambridge (UK), and IST, Technical University of Lisbon, under the supervision of Dr. Sijbren Otto and Prof. Carlos Afonso. In April 2008, he joined Faculty of Science and Technology, New University of Lisbon, as Assistant Research of the Photochemistry and Supramolecular Research Group. His current research interests include the development of supramolecular materials with potential application as host−guest and photochemistry systems and the development and application of new ionic liquids including the chiral ones.

each citizen for a more responsible use of global resources. Similarly in industry and in particular for chemical industry, due to their tremendous impact in our society, there is also constant pressure to reduce costs and consumable resources and have less detrimental impact to the environment. While in the past the main issue was process economics, nowadays the preferred process is frequently the more environmentally friendly one mainly due to more restricted environmental

Pedro M. P. Gois was born in Lisbon (Portugal) in 1977. He studied chemistry at the New University of Lisbon from where he also received in 2005 his Ph.D. in organic chemistry under the supervision of Prof. Dr. Carlos Afonso. From May 2005 to May 2008, he worked as a postdoctoral research fellow at the University of Sussex with Prof. Dr. F. Geoffrey N. Cloke, FRS, at the University College of London with Prof. Dr. Stephen Caddick, and at the Instituto Superior Técnico (Technical University of Lisbon) with Prof. Dr. Carlos Afonso on the development of novel organic transformations catalyzed by new N-heterocyclic carbene rhodium and palladium complexes. In May 2008, he joined the Pharmacy Faculty of the Lisbon University as an assistant research fellow of the medicinal chemistry group (iMed.UL, Research Institute for Medicines and Pharmaceutical Sciences). His research encompasses the study of multicomponent reactions, the use of water as a reaction medium, the development of new methodologies mediated by metal or organocatalysts, and the synthesis of small molecules with potential activity against Alzheimer's and Parkinson's diseases. In 2001, he received a school merit award in chemistry from the Faculty of Sciences and Technology of the New University of Lisbon, and in October 2008, he received an Honor Mention in the Young Research Award of the Deloitte/Technical University of Lisbon.



Carlos A. M. Afonso graduated from University of Coimbra (1984), and he joined the New University of Lisbon as teaching assistant and received his Ph.D. in 1990 under the supervision of Professor C. D. Maycock where he became assistant professor. He worked for one year as postdoctoral fellow at the Imperial College of Science Technology and Medicine under the supervision of Professor W. B. Motherwell (1990) and one more academic year of sabbatical leave (1997−1998) at the University of Bath, U.K. (Professor J. Williams), and at the University of Toronto (Professor R. Batey). In 2004, he moved to Instituto Superior Técnico of the Technical University of Lisbon as associate professor, and in 2008, he received his *Agregação*. His research focuses on the development of more sustainable methodologies in asymmetric organic transformations and the development and application of new ionic liquids.

regulations and high costs of waste treatment, removal, and remediation.[1] This pressure in industry also gives an extra impetus to discover more environmentally friendly synthetic approaches in different research areas.[2,3] Solvent reaction media and separation processes are important issues in the

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context of more sustainable chemistry, which appear in the twelve principles of Green Chemistry described by Anastas and Warner[4] and in the main topics selected by James Clark for the *Clean Technology Pool:* intensive processing, alternative routes, life cycle assessment, supercritical solvents, microreactors, renewable feedstocks, telescoped reactions, nonvolatile solvents, catalysis, alternative energy savers and solventless systems.[5] From an economic point of view, the capital and operation costs due to separation processes are usually in the range of 60−80% of the overall costs.[6] In many well established chemical processes with major emphasis in the pharmaceutical industry, considerable amounts of organic volatile compounds are used as reaction media and for separation. In this context, the development of new reaction media and product isolation methods that allow the reduction of volatile organic solvents is certainly appealing to achieve more sustainable chemistry. In addition, if the new reaction media provides some benefit on the reaction performance such as on the regio-, diastereo-, and enantioselectivity, catalyst efficiency, and catalyst reuse when applied, this is certainly very appealing. Heterocycles are molecules extremely important in different areas, including medicinal chemistry. Here an overview of the open literature on the development of more sustainable methodologies for the synthesis of N-based heterocycles based on solvent-free and fluorous-tag approaches and by the use of water, poly(ethylene glycol) (PEG), ionic liquids, fluorinated fluids, and supercritical CO_2 as solvents for reactions or separation is provided. Since the main goal of this review is to enable the readers to follow new methods toward heterocyclic compounds synthesis, it is divided according to ring simplicity and subdivided by the number of nitrogen atoms contained in the ring. The modification of compound side chains is also covered in this work, being referenced in the section relative to the corresponding main heterocycle skeletons.

1.1. Solvent-Free Transformations

Since the last two decades of the 20th century, there has been a growing demand for the development of more sustainable chemistry, particularly in the synthesis of highly valuable products, in order to minimize the great amounts of waste and consecutive treatment. One of the greatest contributions to this waste volume is the volatile components used as solvents in the synthetic steps and sequential purification of the desired compound(s). The use of solvents in organic synthesis reactions has been classified as indispensable due to its role in facilitating the heat transfer of the reaction mixture with the neighborhood, promotion of diffusion of the molecules along the reaction vessel, and decreasing the difficulty of reagent or product transfers.[7] Nowadays, it is well known that reactions can occur in the solid phase, being in most cases more selective (due to the arranged crystal lattice) and more efficient than in liquid phase reactions.[8] Despite all that, we still assume that the use of solvent is indispensable in organic synthesis.

Reactions in solvent-free conditions (SFC) have been seen as an excellent way to minimize the above-mentioned waste. Furthermore, the use of SFC has several advantages compared with classic conditions:

- reduced risks inherent to the use of high amounts of volatile organic solvents
- no need to recover, purify, and reutilize the solvent, reducing the pollution arising from such operations
- easy recovery of the support in cases where an inorganic support (such as silica, alumina or clays) is used
- in most cases attainment of the desired products in sufficient purity to avoid time consuming chromatography or even recrystallizations, simplifying the synthetic steps
- in most cases more rapid reaction of reagents
- ability to perform sequential reactions in high yields and obtain large compounds libraries
- no need to use proper materials
- avoidance of protection and deprotection of reactive functional groups
- more economically appealing scale-up procedures for industry, because of the lack of solvent and the smaller apparatus required.

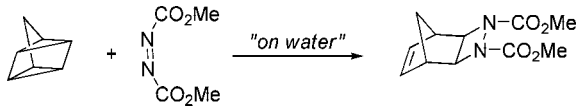
Microwave irradiation methodology in organic synthesis produced enormous impact on SFC reactions. Indeed, there are several publications covering these techniques with most of them relating SFC and microwaves.[9−19] This preference for SFC in the use of microwaves is mainly due to easier observation of the marked microwave effect because there can be radiation losses due to the dielectric constant of the solvent, more profitable employment of silica, alumina, or clays under SFC (due to their great capacity to absorb microwave radiation than solvent), minimization of explosion risks from volatile organic compounds, and ability to use phase transfer catalysts.

The sections of this review devoted to solvent-free reactions aim to cover all the synthetic methodologies developed since 1995 through the use of solvent-free conditions. Since reactions performed under microwave irradiation are usually done in the absence of solvent, in most of cases using inorganic supports, they are also covered in this work.

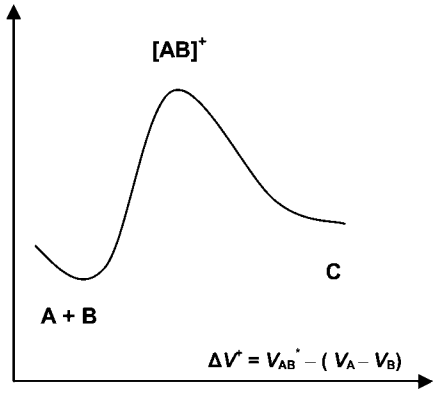
1.2. Water as a Solvent

Nature, the most amazing entity of the universe, assembled truly complex molecules with astonishing efficiency from a primordial aquatic environment. This creation is the base of what we refer to as Life, the most complex form of organic and inorganic compounds on Earth. Therefore is without surprise that we witness the efforts of numerous research groups to introduce water as solvent in many organic transformations. This recent interest stems from environmental, economic, and chemical reasons. Obviously, water is the most desirable solvent available because it is abundant,

Scheme 1



Scheme 2



inexpensive, and safe. Nevertheless, water notoriety does not end with this *green relevance*; water is one of the most fascinating liquids on Earth and quite often exerts a remarkable influence over the chemical transformations performed in this media. Over the last decade, as bystander to an explosion of research activity on the use of water, a substantial contribution was in fact made by the endeavours of Green Chemistry.[20,21]

The seminal work of Breslow on the influence of water over pericyclic reactions triggered the enthusiasm of the chemical community. Breslow discovered that Diels−Alder reactions proceed faster in water (as high as 700-fold) and with a higher *endo*/*exo* selectivity than in organic solvents. This remarkable influence of water over pericyclic transformations popularized the hydrophobic effect, which occurs when nonpolar solutes immiscible with water are dissolved/suspended in water, this creates a cavity in the ordered structure of water, which reorganizes around the solute creating what as been called a clathrate.[22−24]

Generally, water is considered as solvent in a reaction when it partially solubilizes the reactants prone to react. This notion was recently updated with the work of Sharpless, in which the concept of reactions "on water" was introduced. This new expression indicates reactions of organic substances that are not soluble yet react well or even considerably faster in water than in organic solvents (Scheme 1).[25]

It is deceptive to pretend that there is a common explanation for the exact role of water as solvent; nevertheless, as Breslow's observation clearly indicates, water appears to accelerate reactions in which the transition state molar volume is significantly lower than the reactants; Diels−Alder reactions and Claisen rearrangements are examples of transformations favored by the presence of water (Scheme 2). Furthermore, the small size and high polarity of a water molecule, as well as a three-dimensional hydrogen-bonded network system of bulk water (Scheme 2), provide some unique properties, among which the large cohesive energy density (about 550 cal/cm^3), a large surface tension (72 dyn/cm), and a large heat capacity are particular noteworthy.[22−24,26,27] In addition and in accord with a recent study disclosed by Marcus et al.,[28] in the case of on-water reactions, there is a key aspect that distinguishes them from aqueous homogeneous or neat reactions. In the structure of water at the oil−water interface of an oil emulsion, approximately one in every four interfacial water molecules has a free OH group that protrudes into the organic phase enabling catalysis via the formation of hydrogen bonds. This presents an explanation for the striking rate increase, reported by Sharpless, in reactions carried out on water.

The use of water as solvent is particular advantageous in those cases where tedious protection−deprotection reactions may be avoided; carbohydrate chemistry is a notable example of this. Furthermore, the low solubility of oxygen gas in water enhances the potential of this media as solvent for oxygen-sensitive catalyzed processes. Finally, but not less important, water offers an additional advantage over traditional organic solvents in that it allows the reutilization of water-soluble catalysts after extraction of water-insoluble reaction products.[29]

The unique physical and chemical properties of water, makes this liquid a suitable and in some cases extremely useful medium for a wide range of chemical transformations. The following list highlights some of the areas in which water has proven its utility:[29−31]

- pericyclic reactions
- reactions of carbanions
- reactions of carbocations
- reactions of radicals
- reaction of carbenes
- transition-metal catalysis
- oxidations and reductions
- carbohydrate chemistry

Some excellent reviews have been published concerning the synthesis of organic molecules using water as solvent,[20,21,32] though to our knowledge none cover specifically the synthesis of heterocycles in aqueous media. Therefore it is the aim of the present review to gather and discuss the open information regarding the synthesis of heterocycles using water as solvent because they represent one of the most important classes of organic molecules present in most life forms on Earth.

Microwave-assisted synthesis (MAS) of heterocycles in water has become an exciting research topic, which was recently reviewed by Kappe et al., and for this reason, MAS will not be extensively discussed in this review.[19]

1.3. PEG as Solvent

Poly(ethylene glycol) (PEG) is the linear polymer formed from the polymerization of ethylene oxide and has many applications, not only in chemistry but also in other diverse disciplines as well.

Several types of PEG are available for purchase depending on the size and terminal functional groups, for example, OH-PEG-OH or MeO-PEG-OH. Generally smaller sized polymers like PEG_{200} or PEG_{400} (MW of 200 and 400, respectively) are liquid at room temperature and are generally applied as solvent.[33,34] High-weight PEGs (like PEG_{4000}) are solid at room temperature but become liquid at 61 °C and are generally applied as supports in soluble polymer-supported chemistry.[35−37]

PEG polymers are soluble in relatively polar solvents like dimethylformamide, methanol, and water but are insoluble in diethyl ether or isopropanol. This property allows the recovery of such macromolecules by precipitation and filtration, which is extremely important in soluble polymer-supported chemistry. PEGs are viewed to possess the main advantages of homogeneous and heterogeneous systems.

PEGs have become very popular in organic synthesis since they are nonvolatile, recyclable, stable to acid, base, and high temperature, and available in high quantities at low prices. Furthermore, their well-known low toxicity makes them greener versions of conventional halogenated solvents.[38]

The fast growth of published works about PEGs in medicinal areas reflects the importance of PEG polymers mainly related to their low toxicity (biocompatibility). PEGs can enhance the solubility of hydrophobic drugs increasing their bioavailability.[39,40]

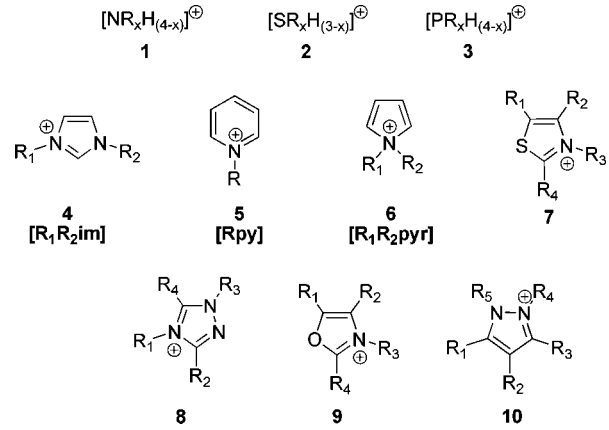
1.4. Ionic Liquids As Solvent

The history of the development of modern science of chemistry is marked by dramatic increases in the variety of compounds, products, and synthesis paths. Today, some tens of thousands of compounds are used commercially in large amounts, and a significant proportion of these chemicals are also released into the environment. Both industrial and academic chemists thus have a significant responsibility in designing scientific and industrial approaches that are more sustainable. The concept of sustainable chemistry is commonly defined as chemical research aiming at the optimization of chemical processes and products with respect to material and energy consumption, toxicity, inherent safety, environmental degradability, and so on. In this context, green chemistry can be an important key in order to produce cleaner and efficient synthetic processes.[41]

In recent years, ionic liquids (ILs),[42−44] which consist of organic cations and appropriate anions (liquid compounds until 100 °C), have received much attention due to their potential as alternative recyclable environmentally benign reaction media for chemical processes. They have intrinsically useful properties, such as thermal stability, high ionic conductivity, negligible vapor pressure, and a large electrochemical window. Depending on the anion and the alkyl group of the imidazolium cation, the ILs can solubilize carbonyl compounds, alcohols, alkyl halides, supercritical CO_2 ($scCO_2$), and also transition metal complexes.[45,46] Furthermore, they can have low miscibility with dialkyl ethers, alkanes, and water and can be insoluble in $scCO_2$.[47]

ILs can be called "designer solvents"[48] because their physical properties (such as melting point, viscosity, density, and hydrophobicity) can be modified according to the nature of the desired reactions by modification of their cations and anions.[49] Generally, ILs mainly comprise organic cations such as tetra-alkylammonium (**1**),[50] trialkylsulfonium (**2**),[51] tetra-alkylphosphonium (**3**),[52] 1,3-dialkylimidazolium (**4**),[53] *N*-alkylpyridinium (**5**),[54] *N*,*N*-dialkylpyrrolidinium (**6**),[55] *N*-alkylthiazolium (**7**),[56] *N*,*N*-dialkyltriazolium (**8**),[57] *N*,*N*-dialkyloxazolium (**9**),[58] and *N*,*N*-dialkylpyrazolium (**10**)[59] combined with several organic or inorganic anions (Scheme 3). Most ILs are based on heterocyclic compounds, particularly, the 1,3-dialkylimidazolium or 1-alkylpyridinium cations, which can be prepared first by quaternization reaction with an appropriate alkyl halide and then the exchange of the halide anion for the desired anion using the corresponding salt or acid. Despite the excellent coverage on the topic recently by Martins and co-workers,[60] here is presented another overview of transformations involving heterocyclic synthesis using ILs as alternative reaction media.

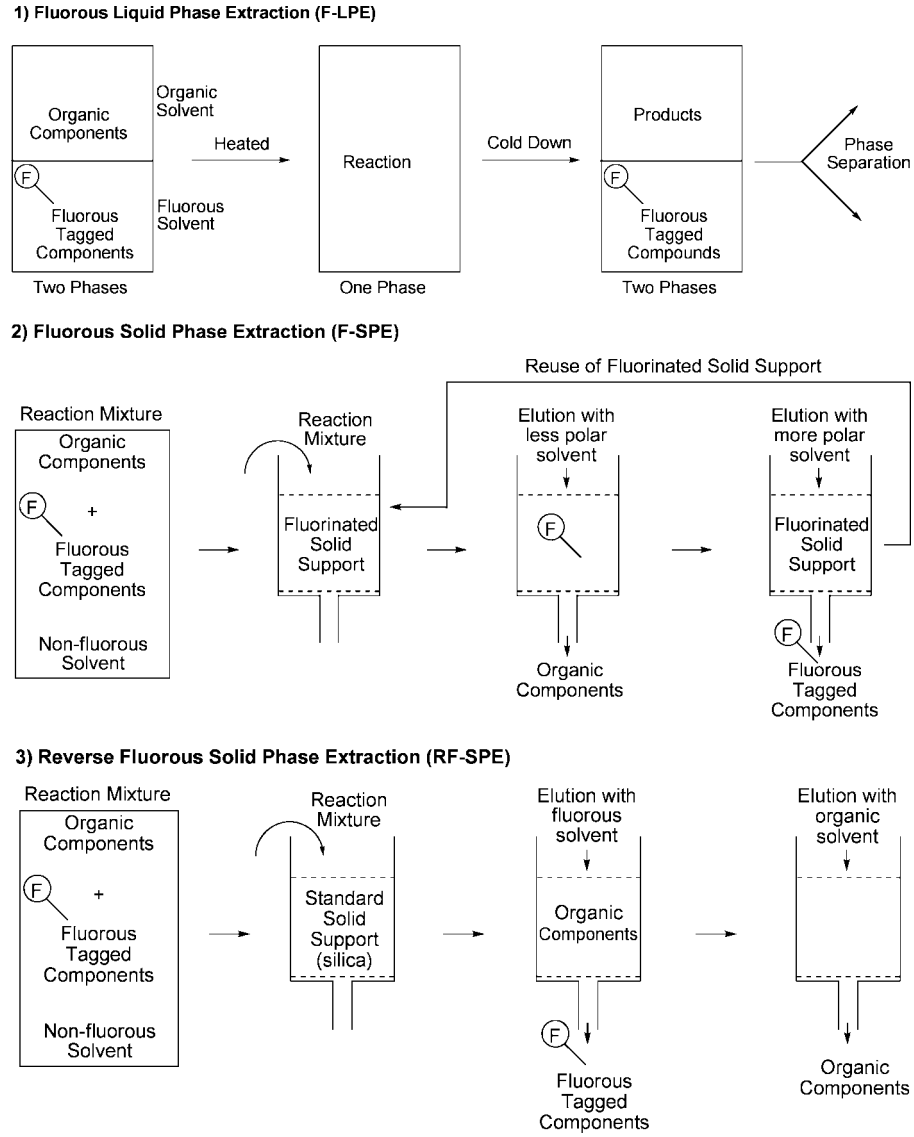
Scheme 3



1.5. Fluorinated Solvents and Fluorous Tags

The unique affinity and chemically inert properties of perfluorinated alkyl chains allows the development of new phase separation techniques as has been elegantly pointed out by Vogt[61] and Harváth and Rábai.[62] Perfluoroalkanes present preferential fluorine−fluorine interaction and low interactions with water, protic and polar solvents, hydrocarbons, and common fuctionalized organic compounds. This property allows the development of efficient combinations of reaction and separation techniques with considerable advantages for catalytic reactions, allowing the development of efficient processes for catalyst reuse.[63−65] The pioneering approach was based on a fluorous liquid-phase extraction (F-LPE) system consisting of organic solvents, fluorinated solvents and reagents, and frequently catalysts in which some of the constituents were highly fluorinated. By heating the system, one phase is formed, allowing the occurrence of the reaction under more advantageous homogeneous conditions. After cooling, two phases are again generated allowing simple separation of products according to their partition between organic and fluorinated phases (Scheme 4). This approach has been elegantly used for a considerable number of key organic transformations.[63,66−68] However, the biphasic system presents the main disadvantage of use of fluorinated solvents, which are more expensive and present considerable environmental concerns due to their ozone-depletion potential.[69] To circumvent this limitation,[70,71] other approaches were developed among which the most used system is based on standard fluorous solid-phase extraction (F-SPE) in which no fluorinated solvent is needed and automation is feasible (Scheme 4).[72,73] In this system, the component containing the fluorous tag is preferentially retained in the fluorinated solid support allowing separation from other nonfluorinated components just by adjusting the eluent solvent polarity.[74] Another related approach is based on reverse F-SPE in which the fluorinated solvent is still required.[75] Another system has been reported based on the use of Teflon tape for catalyst reuse.[76] Apart from several reviews covering this area,[63,77−79] Zhang in 2003 provided one review focused on fluorous synthesis of heterocyclic systems in which the separation approach based on fluorous tags was also covered.[80] More recently (2006), Zhang and Curran provided an overview of the reported transformations, commercially available set-ups, and practical features of the use of F-SPE approaches.[75] Here is provided an overview of the reported examples in which the use of fluorous tags presents considerable advantages for the overall process of synthesis of heterocycles.

Scheme 4. Illustration of Representative Reaction and Separation Approaches Based on the Use of Fluorous Tags in (1) Fluorous Liquid-Phase Extraction (F-LPE), (2) Fluorous Solid-Phase Extraction (F-SPE), and (3) Reverse Fluorous Solid-Phase Extraction



1.6. Supercritical CO_2

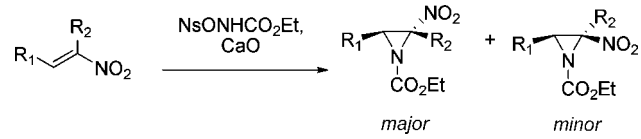
Supercritical CO_2 ($scCO_2$) is an unconventional solvent that differs from ordinary solvents due to the gas-like low viscosity and high diffusivities and liquid-like solubilizing power. Additionally, these properties are readily tunable by changing the operating temperature and pressure. $scCO_2$ has the added benefits of an environmentally benign nature, nonflammability, low toxicity, and high availability.[81−83] These properties allow the application of $scCO_2$ in different areas such as extraction, chromatography, material processing, and reactions including enzymatic ones.[84] Many organic reactions, including asymmetric and symmetric catalyzed ones, have been developed using $scCO_2$ as an efficient solvent for product separation and catalyst reuse.[81,83,85] In some of these synthetic transformations, heterocyclic substrates have been used.

2. Three-Membered Rings

2.1. Solvent-Free Reactions

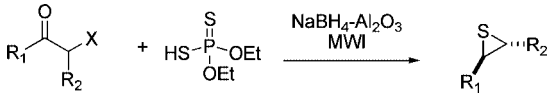
Aziridines are three-membered-rings and therefore the smallest heterocyclic structure. They are a well-known class of compounds, their unique structure produces an enormous potential as intermediates for organic synthesis, and moreover, they frequently displaying potent and diverse biological activity.[86]

Scheme 5



The preparation of the simplest N-heterocycles, aziridines, can be accomplished by aziridination of conjugated (*E*)-nitroalkanes with ethyl [(4-nitrobenzenesulfonyl)oxy]carbamate in presence of CaO inorganic base. The procedure simply consists of grinding the reagents together with the substrate in a mortar, yielding preferentially the desired aziridine with the same configuration as the substrate (Scheme 5). Despite the uncertainty related to the reaction mechanism, the authors point toward an aza-Michael addition of the anion generated followed by ring closure by elimination of NsO^-.[87]

Table 1



entry	R_1	R_2	X	reaction time (min)	yield (%)	*trans*/*cis*
1	Me	H	Cl	2.0	88	
2	Me	Me	Cl	3.0	85	91:9
3	Me	Me	Br	3.0	88	91:9
4	Et	Et	Cl	3.5	86	93:7
5	*t*-Bu	*t*-Bu	Cl	4.0	81	89:11
6	Ph	H	Br	2.5	94	
7	Ph	H	Cl	2.5	92	
8	cyclohexanone		Cl	3.5	84	0:100
9	cyclohexanone		Br	3.5	86	0:100
10	4-ClC_6H_4	4-ClC_6H_4	Br	3.0	94	96:4
11	4-MeC_6H_4	4-MeC_6H_4	Br	3.0	90	94:6

Recently, in order to avoid the use of toxic and expensive transition metal catalysts, *N*-methylpyrrolidin-2-one hydrotribromide was employed as an efficient catalyst in the aziridination of alkenes using chloramine-T as the nitrene donor. Several aziridines can be obtained in good to excellent yields (65−92%) in a room temperature solvent-free reaction.[88] For the introduction of a N-substituent, Attanasi et al. recently reported the efficient 1,4-conjugate addition of aziridines to the azo−ene system of 1,2-diaza-1,3-butadienes under SFC at 65 °C. The diastereoisomeric mixture of α-aziridinohydranones formed were then converted to imidazoles in toluene reflux.[89]

For the preparation of three-membered S-heterocycles, thiiranes, an efficient one-pot procedure has been described. The reaction of α-halo ketones with *O*,*O*-diethyl hydrogen phosphorodithioate in the presence of alumina-supported sodium borohydride under microwave irradiation led to the formation of the desired thiiranes in good yields and high diasteroselectivities (Table 1).[90]

2.2. Reactions in Aqueous Media

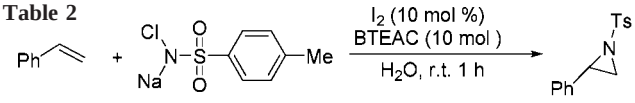
Bearing in mind the synthesis of three-membered-rings, Komatsu et al. reported the first aziridination of olefins under phase-transfer conditions using a chloramine-T−I_2 system. In the presence of a catalytic amount of quaternary ammonium salts, a variety of olefins were successfully aziridinated in moderate to excellent yields (Table 2). In this system, benzyltriethylammonium chloride (BTEAC) and Aliquat 336 proved to be the most efficient phase-transfer agents, even when used in catalytic amounts.[86]

An efficient synthesis of optically active aziridines was presented by Bieber et al. starting from chiral amino alcohols. In this study, two complementary one-pot procedures for the preparation of *N*-tosyl aziridines from 2-amino alcohols were disclosed. In method A, acetonitrile was used as solvent, whereas in method B, a biphasic system of water/dichloromethane was used.[91]

The results presented in Table 3, show that the less hindered amino alcohols can be converted efficiently using potassium hydroxide in a biphasic water/dichloromethane system (method B), while higher substituted amino alcohols give better yields in an organic system using potassium carbonate as the base.[91]

In a recent report, an efficient and highly selective synthesis of bicyclic-α-keto aziridines was presented. This procedure is based on the reaction of 2-bromo-cyclopentanones and aliphatic primary amines mediated by phase transfer catalysts (PTCs) in water at room temperature. Carlson et al., after an extensive screening of PTC reagents, identified tetrabutylammonium bromide (TBAB) as the most suitable catalyst for this transformation in water (Table 4).[92]

Table 2



2 mmol 1 mmol 96 %

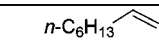
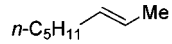
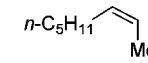
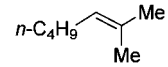
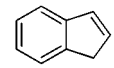
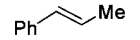
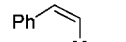
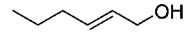
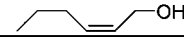
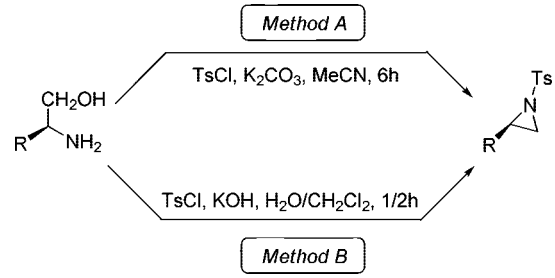
Entry	Olefin	I_2/mol (%)	Time (*t*/h)	Yield (%) (*cis*:*trans*)
1		20	5	77
2		15	5	52 (<5:>95)
3		15	5	81 (>95:<5)
4		10	5	43
5		20	3	74
6		20	2	56
7		10	1	87 (25:75)
8		10	5	91 (34:66)
9		30	5	36 (>95:<5)
10		10	3	79 (<5:>95)
11		10	3	72 (>95:<5)

Table 3

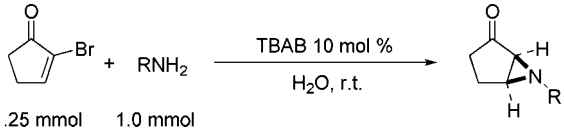


entry	R	method A yield (%)	method B yield (%)
1	H	46	74
2	CH_3	53	78
3	C_2H_5	62	86
4	$(CH_3)_2CH$	75	70
5	$CH_3CH_2CH_2$	82	73
6	$(CH_3)_2CHCH_2$	76	52
7	$C_6H_5CH_2$	92	64
8	$CH_3SCH_2CH_2$	85	67
9	4-HO-$C_6H_4CH_2$	87	58

2.3. Reactions in PEG or PEG Tag Approaches

The thiiranes are three-membered rings containing only one heteroatom, a sulfur atom. This family of heterocycles is generally prepared by reacting oxiranes with a nucleophilic sulfur source in the presence of a metallic Lewis acid catalyst. Recently Das et al. demonstrated that poly(ethylene glycol) can play a double role in this transformation.[93] Besides its application as a green solvent with good recyclability, it eliminates the need to use a metallic Lewis acid. The possibility of hydrogen bonding with the oxiranes allows their activation and therefore their smooth conversion to thiiranes

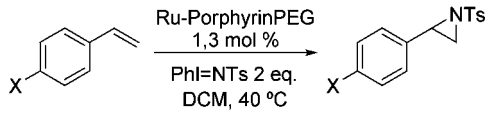
Table 4



1.25 mmol 1.0 mmol

entry	R	time (h)	yield (%)
1	CH_2Ph	5	98
2	CH_2CH_2Ph	5	93
3	CH_2furyl	5	91
4	cyclohexyl	3	90
5	$CH_2CH{=}CH_2$	3	96
6	*n*-Bu	3	95
7	*t*-Bu	1	94
8	*n*-Pr	3	97

Table 5



entry	substrate	conversion, %	yield, %	TON
1	X = H	58	88	38
2	X = F	46	76	26
3	X = Cl	62	79	37
4	X = Br	53	80	32
5	X = CH_3	62	88	41
6	2-naphtylstyrene	78	85	50

with excellent yields (89−95% yield for aromatic and aliphatic oxiranes in less than 1 h).

On other hand, three-membered heterocyclic compounds containing one nitrogen atom are called aziridines and can be prepared by the reaction of alkenes with nitrenes mediated by metalloporphyrins. These types of catalyst are very expensive, especially those containing a ruthenium metal center; therefore some efforts have been made to immobilize such complexes. For example, covalent attachment to poly(ethylene glycol) chains allowed catalyst recovery at the end of the reaction maintaining the properties of a homogeneous catalyst.[94,95] This supported catalyst prepared by Che et al. provided moderate conversions and activity in olefin aziridation reactions (Table 5).

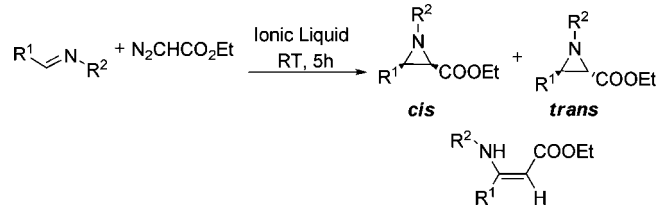
2.4. Reactions in Ionic Liquids

Aziridines are well-known carbon electrophiles capable of reacting with a range of nucleophiles, and their ability to undergo regioselective ring-opening reactions contributes greatly to their synthetic value. The nucleophilic ring opening of aziridine carboxylates leads to many biologically active compounds such as α,β-unsaturated amino acid esters, β-lactam antibiotics, and alkaloids.[96]

Recently, bismuth(III) triflate has been used in an ionic liquid as a recyclable catalytic system for the synthesis of *cis*-aziridine carboxylates through the one-pot coupling of aldehydes, amines and ethyl diazoacetates.[97]

Several groups have developed general methodologies for one-step formation of aziridines using transition metal catalysts such as chloramine-T (Ts-N-ClNa), bromamine-T (Ts-N-BrNa)[98−100] or [*N*-(*p*-toluenesulfonyl)imino] phenyliodinane (PhI=NTs).[101,102] Recently, the synthesis of aziridines has been reported from reactions of imines with ethyl diazoacetate (EDA) catalyzed by $Cu(OTf)_2$,[103] $Ln(OTf)_2$,[104] several other Lewis acids,[105,106] and methylrhenium trioxide.[107]

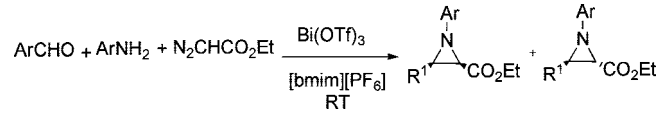
Table 6



				yield, %	
entry	ionic liquid	R^1	R^2	aziridine	enamine
1	[bmim][BF_4]	Ph	Ph	82, *cis*/*trans* = 29.6:1	3
2	[bmim][PF_6]	Ph	Ph	95, *cis* only	2
3	[bmim][PF_6]	Ph	Ph	93, *cis* only	3
4[a]	[bmim][PF_6]	Ph	Ph	0	0
5[b]	[bmim][PF_6]	Ph	Ph	0	0
6	[bmim][PF_6]	*p*-MeC_6H_4	Ph	83, *cis* only	8
7	[bmim][PF_6]	*p*-MeC_6H_4	Ph	91, *cis* only	
8	[bmim][PF_6]	*o*-$MeOC_6H_4$	*p*-MeC_6H_4	85, *cis* only	
9	[bmim][PF_6]	*p*-ClC_6H_4	Ph	98, *cis* only	
10	[bmim][PF_6]	*o*-ClC_6H_4	Ph	97, *cis* only	
11	[bmim][PF_6]	*p*-$NO_2C_6H_4$	Ph	98, *cis*/*trans* = 33.7:1	
12	[bmim][PF_6]	*p*-BrC_6H_4	Ph	98, *cis* only	

[a] Used dichloromethane as co-solvent. [b] Used hexane as co-solvent.

Scheme 6



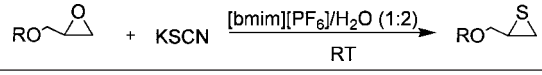
Xia et al. reported a convenient synthesis of aziridines from imines and EDA in ionic liquids at room temperature **(**Table 6).[108] Using [bmim][PF_6] and [bmim][BF_4] as reaction media allowed preparation of several aziridines in high yields with *cis* selectivity. For most of the reactions studied, only *cis*-aziridines were isolated without detectable amounts of the carbene-coupling product.

Arylimines with either electron-donating or electron-withdrawing groups react efficiently with EDA in [bmim][PF_6] affording the corresponding aziridines with high *cis* selectivities. The authors suggested that the formation of aziridines in ionic liquids proceeds by a similar mechanism to the one previously proposed for typical Lewis acids. After each reaction using ionic liquids as reaction media, the products were extracted with petroleum ether and ethyl acetate (5:1). The ionic liquid [bmim][PF_6] was easily recycled five times with good conversions and high *cis* selectivities observed.

Yadav et al. described another approach using bismuth(III) triflate in IL [bmim][PF_6] as a recyclable catalytic system for the synthesis of *cis*-aziridine carboxylates through the one-pot coupling of aldehydes, amines, and ethyl diazoacetates (Scheme 6).[97]

Thiiranes were synthesized in high yields from a variety of epoxides with potassium thiocyanate using a biphasic solvent system of [bmim][PF_6]/water (2:1).[109] The use of ionic liquids for this transformation avoided the presence of heavy metal halides as promoters and chlorinated hydrocarbons as solvents. Yadav et al. demonstrated that water addition (1 equiv) to the ionic liquid improved the reaction rate, as well as the yield, probably due to the higher solubility of potassium thiocyanate in water. Among the two ionic liquids reported, [bmim][PF_6] was found to be superior in terms of conversion (Table 7).

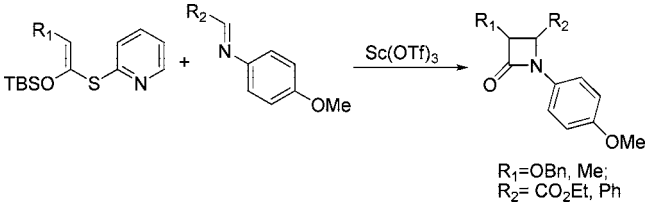
Table 7



			[bmim][PF_6]/H_2O		[bmim][BF_4]/H_2O	
entry	R	conversion (%)[a]	time (h)	yield (%)[b]	time (h)	yield (%)[b]
1	Ph	100	3.5	95	4.5	91
2	Allyl	99	3.0	92	5.0	85
3	*n*-Bu	97	4.5	90	6.0	87
4	*p*-*t*-BuC_6H_4	100	4.0	89	5.5	83
5	*p*-ClC_6H_4	100	3.5	96	4.0	85
6	*p*-MeOC_6H_4	100	3.0	92	5.5	89
7	PhCO	99	5.0	85	7.0	85
8	*p*-MeC_6H_4	100	4.5	95	5.5	90

[a] Conversions were determined by GC analysis. [b] Yield refers to the isolated pure products after column chromatography.

Scheme 7



The reaction conditions were mild enough not to induce isomerization of C−C multiple bonds during the preparation of thiiranes bearing propargylic and allylic functionalities and also selective enough to convert oxiranes into thiiranes in the presence of acid-sensitive groups. The ionic liquid was recycled five to six subsequent cycles although the authors observed gradual decrease in activity.

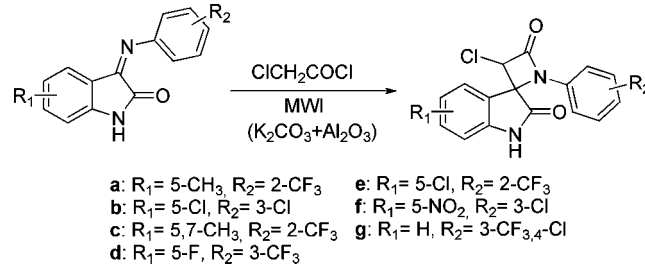
3. Four-Membered Rings

3.1. Solvent-Free Reactions

β-Lactams are widely recognized representatives of this class of heterocycles. Over the last decades, this class of antibiotics provided an invaluable line of defence against bacterial infections and other life-threatening illnesses.[110] Among the many different families of β-lactams known, the vast majority have a fused bicyclic framework; nevertheless, recent studies demonstrated the high biological activity of a considerable array of monocyclic β-lactams. The synthesis of such units, in particular, the mono-β-lactams, is well-documented using water/organic solvents as the reaction medium.[110]

Four-membered rings, β-lactams, can be obtained in good to moderate yields (44−90%) under SFC through ring closure of azadienes under microwave irradiation (MWI). In this case, the Staudinger reaction of *N*-trialkylsilyl-substituted azadienes (protected with the TBDMS group in order to minimize substrate decomposition) can be performed under microwave irradiation for 3 min to give the desired lactam in the same diasteroselectivity as the reaction performed in toluene.[111] Recently, Benaglia et al. reported the use of $Sc(OTf)_3$ as catalyst for the room-temperature solvent-free synthesis of β-lactams (Scheme 7). After a 20 h reaction between ethyl glyoxolate derivatives and silyl ketene thioacetal (2 equiv) in the presence of 1 mol % catalyst, the desired lactam can be obtained (as a diastereoisomeric mixture) in reasonable to good yields (45−71%). According to the authors, scandium(III) triflate plays a dual role, activating the imine toward attack of the carbon nucleophile and promoting the ring-closing step, with this last occurring if the catalyst is present in sufficiently high concentration.[112]

Scheme 8



Scheme 9

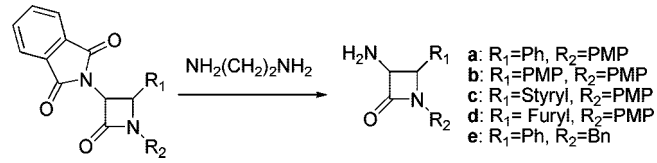
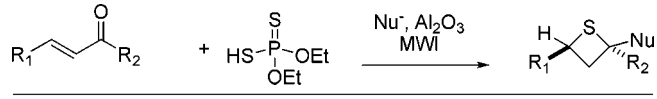


Table 8



entry	R_1	R_2	Nu	reaction time (min)	yield (%)
a	Ph	Ph	CN	3.0	84
b	4-ClC_6H_4	Ph	CN	2.5	87
c	4-ClC_6H_4	4-ClC_6H_4	CN	2.0	92
d	Ph	Ph	MeS	3.5	81
e	Ph	Ph	MeS	3.0	83
f	4-ClC_6H_4	Ph	MeS	2.5	88
g	Ph	Ph	EtS	4.0	77
h	4-ClC_6H_4	Ph	EtS	3.5	80
i	4-ClC_6H_4	4-ClC_6H_4	EtS	3.0	85

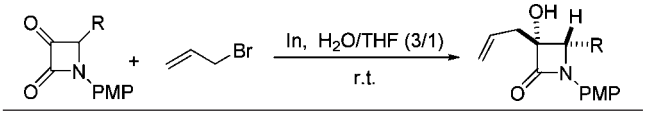
An example of synthesis of some spiro[azetidine-indole]-diones was reported (Scheme 8) through the use of basic alumina-supported potassium carbonate. The MWI-induced cycloaddition of 3-arylimino indolinones with chloroacetyl chloride can be performed by irradiating the reactants for a few minutes allowing the formation of spiro β-lactam in good yields (85−92%).[113]

About the β-lactam substituents, an α-amino group can be deprotected from tetrachlorophtaloyl in good yields (83−99%) by reacting it with ethylenediamine at room temperature for 5 min (Scheme 9).[114] In the solvent-free modification of cephalosporin synthesis, the free amino group of the 7-ACA (7-amino-cephalosporanic acid) can be modified to an amide group in excellent yields (83−93%) by reaction with heterocyclic acids under microwave irradiation for a couple of minutes using basic alumina as an inorganic support.[115]

The N-alkylation of this class of rings was demonstrated for strained bicyclic β-lactams. After deprotonation with cesium carbonate in silica, the addition of an alkyl or aryl halide at room temperature leads to the formation of N-alkylated β-lactams in good yields. It was observed that the use of silica decreases the hygroscopic properties of the inorganic base, increasing the reaction selectivity.[116]

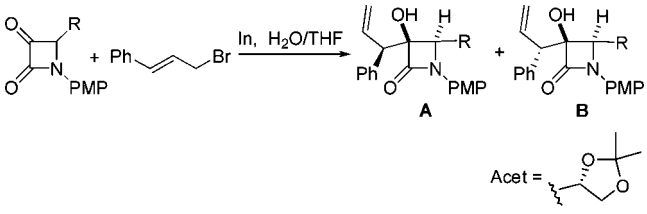
Synthesis of four-membered S-heterocycles, thietanes, can be successfully accomplished using a microwave oven for the nucleophile-induced cyclization of Michael adducts in the presence of *O*,*O*-diethyl hydrogen phosphorodithioate in an alumina bath (Table 8).[117]

Table 9



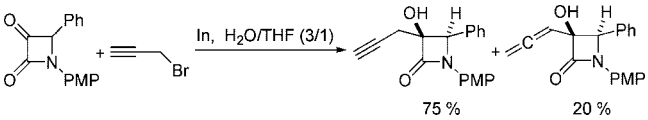
entry	R	time (h)	yield (%)
1	Ph	8	89
2	PMP	12	98
3	styryl	5	77
4	*o*-BrPh	16	83

Table 10



entry	R	time	yield (%)	ratio (A/B)
1	Ph	20 min	94	80:20
2	PMP	2 h	87	81:19
3	styryl	30 min	89	90:10
4	acet	4 h	62	55:45

Scheme 10



3.2. Reactions in Aqueous Media

The indium-mediated[118] reaction of carbonyl-β-lactams with stabilized organic halides under Barbier-type conditions in aqueous media has been the subject of several studies. In 1997 Bose et al. reported the preparation of densely functionalized β-lactams. The high reactivity and exceptional stability of indium[118] allowed the preparation of several lactams in yields up to 98%. As shown in Table 9, when a stoichiometric amount of metal was used, only the *Z* diastereomer was obtained.[119]

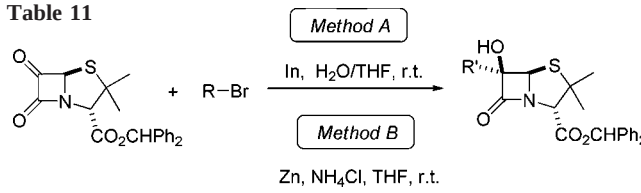
This study was extended to other families of bromides. The addition of cinnamyl bromide yielded the alcohols, in low to high yields with moderate stereoselectivities (Table 10). Hence the reaction of propargyl bromide with azetidine-2,3-dione proceeded with a high level of diastereoselectivity. A single diastereomer was isolated in 75% yield, along with 20% yield of isomerized allene (Scheme 10).[120]

The same methodology was applied by Cho et al. for the preparation of bicyclic β-lactams; the allylation and propargylation of compounds 6-oxopenicillanate (Table 11) and 7-oxocephalosporate (Table 12) yielded the desired products in moderate yields. In this study, a parallel method was tested using a Zn-mediated reaction in anhydrous THF. As shown in Tables 11 and 12, the indium-mediated Barbier reaction in aqueous THF exhibited a slightly higher stereoselectivity than the Zn protocol.[121]

Regarding the stereoselectivity of both protocols, the indium proved to be, to some extent, more effective than zinc. The structure of bromide substrates drastically influenced the product stereoselectivity; for instance, the addition of cinnamyl bromide (Table 11**,** entry 6) resulted in a higher selectivity than addition of crotyl bromide (Table 11**,** entry 5). This fact was explained by the authors in terms of the substituent steric effect considering a pseudo-six-membered transition state (Scheme 11).[121]

This methodology was further explore by Alcaide et al. in the propargylation and allenylation of enantiomerically pure

Table 11



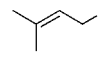
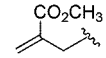
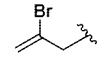
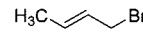
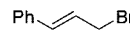
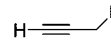
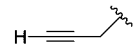
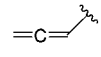
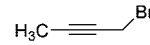
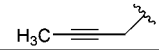
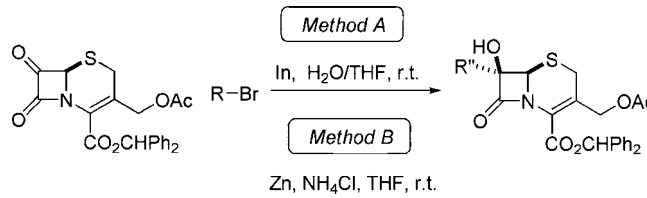
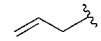
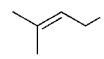
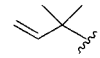
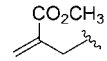
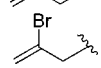
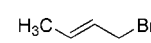
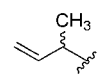
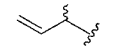
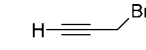
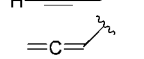
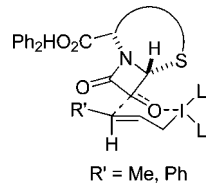
Entry	Bromide	Method	Time (h)	R'	Yield (%)
1		A	1.5		68
		B	2		56
2		A	2		69
		B	2		75
3		A	3		70
		B	4		74
4		A	12		35
		B	9		21
5		A	3		78 (1.5:1)
		B	4		55 (1.3:1)
6		A	3		71 (9:1)
		B	4		70 (4:1)
7		A	3		44 (5:1)
		B	2		71 (40:1)
8		A	3		72
		B	4		65

Table 12



Entry	Bromide	Method	Time (h)	R'	Yield (%)
1		A	1.5		59
		B	4		55
2		A	4		47
		B	2		61
3		A	4		73
		B	4		80
4		A	12		19
		B	12		16
5		A	3		68 (1.5:1)
		B	4		51 (1.3:1)
6		A	3		57 (30:1)
		B	4		61 (12:1)
7		A	3		42 (6:1)
		B	2		55 (40:1)
8		A	3		59
		B	4		55

Scheme 11



azetidine-2,3-diones. To induce enantioselectivity at C-3, a chiral substituent was introduced at C-4, and an extensive study, considering the metal promoter and reaction conditions, was conducted. In this study, the Zn-mediated reaction afforded the highest diastereoselectivity and a reasonable overall yield of 70% of β-lactam. Interestingly, the same metal in a solvent system without water (Table 13, entry 2) resulted in remarkable erosion of the product yield.[122]

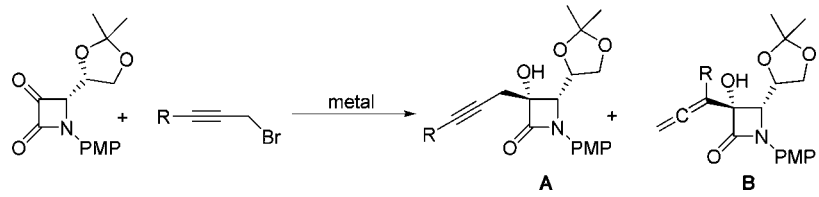
Regarding the allenylation reaction, the presence of an aliphatic or aromatic substituent at the propargyl bromide terminal position resulted in the formation of homoallenyl alcohols with an impressive regio- and diastereoselectivity (Table 13, entries 5−13).

This difference in the selectivity between the propargyl bromide and the substituted propargyl bromides was rationalized by considering the structural differences in the organometallic species involved in the reaction. The authors postulated a metallotropic rearrangement between the propargyl−metal and the allenyl−metal species. Because both intermediaries are able to react with starting azetidine-2,3-dione through a six-membered transition state, the difference arises from the stability exerted by the subsistuents on the propargyl substrate (Scheme 12).[122]

Subsequently, this study was extended to the allylation of enantiomerically pure azetidine-2,3-diones. An extensive study was conducted, including the test of different metal mediators, which afforded diastereoselectivities up to 100% in moderate to excellent yields. Furthermore, in this study the long reaction time, widely recognized as the main drawback of Barbier-type C−C bond formation, was minimized by the addition to the aqueous phase of some additives such as ammonium chloride, indium trichloride, and hafnium chloride (Table 14).[122−126]

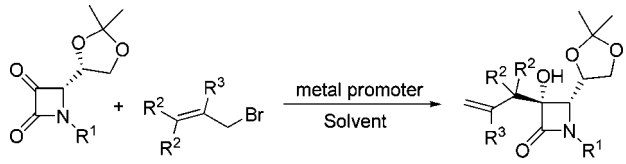
Considering the methodologies that enable four-membered ring construction, Pirrung et al. reported a multicomponent reaction that leads to the formation of β-lactam. This reaction proceeded with remarkable effectiveness affording this heterocyclic in 95% yield. This reaction took 3 h to reach

Table 13



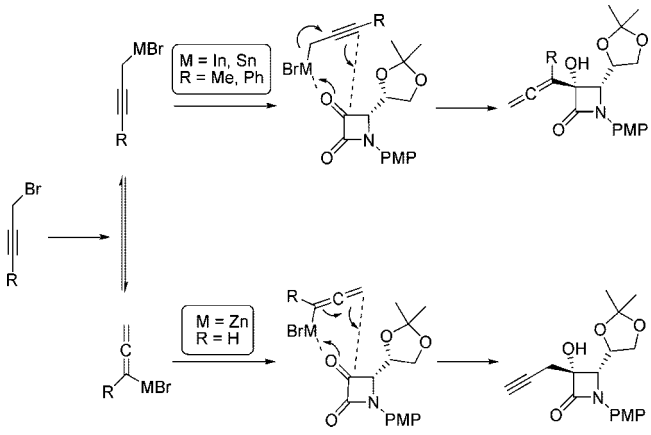
entry	R	metal	solvent system	ratio (A/B)	yield (%)
1	H	Zn	THF/NH_4Cl (aq sat.)	100:0	70
2	H	Zn	THF/NH_4Cl (solid)	100:0	34
3	H	In	THF/NH_4Cl (aq sat.)	71:29	67
4	H	In	THF/H_2O	42:58	50
5	Me	Zn	THF/NH_4Cl (aq sat.)	0:100	59
6	Me	In	THF/NH_4Cl (aq sat.)	0:100	74
7	Me	Sn	THF/NH_4Cl (aq sat.)	0:100	16
8	Me	In	THF/NH_4Cl (aq sat.)	0:100	63
9	Ph	Zn	THF/NH_4Cl (aq sat.)	20:80	71
10	Ph	Zn	THF/H_2O	0:100	16
11	Ph	In	THF/NH_4Cl (aq sat.)	0:100	76
12	Ph	In	THF/H_2O	0:100	75
13	Ph	Sn	THF/NH_4Cl (aq sat.)	0:100	75

Table 14

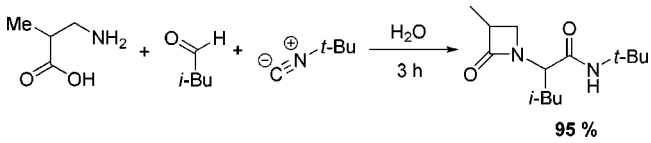


entry	R^1	R^2	R^3	metal promoter	conditions	solvent system	yield (%)
1	PMP	H	H	$Mg/BiCl_3$	20 °C, 18 h	THF/H_2O	72
2	PMP	H	H	In	20 °C, 18 h	THF/H_2O	73
3	PMP	H	H	In	0 °C, 3 h	THF/NH_4Cl (aq sat.)	73
4	PMP	H	H	Zn	20 °C, 18 h	THF/H_2O	72
5	PMP	H	H	Zn	0 °C, 3 h	THF/NH_4Cl (aq sat.)	72
6	PMP	H	H	$In/InCl_3$	20 °C, 2 h	THF/H_2O	73
7	PMP	H	H	$In/HfCl_4$	20 °C 1.5 h	THF/H_2O	73
8	PMP	H	H	$Zn/HfCl_3$	20 °C, 2 h	THF/H_2O	75
9	PMP	H	H	$Zn/HfCl_4$	20 °C, 6 h	THF/NH_4Cl (aq sat.)	75
10	PMP	H	H	Sn	0 °C, 1 h	THF/NH_4Cl (aq sat.)	71
11	PMP	H	CO_2H	In	0 °C, 1.5 h	THF/NH_4Cl (aq sat.)	83
12	PMP	H	CO_2H	Zn	0 °C, 1.5 h	THF/NH_4Cl (aq sat.)	53
13	PMP	CH_3	H	Zn	0 °C, 1.5 h	THF/NH_4Cl (aq sat.)	85
14	3-butenyl	H	H	In	0 °C, 1 h	THF/NH_4Cl (aq sat.)	100

Scheme 12



Scheme 13

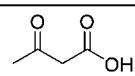
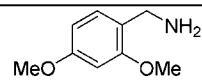
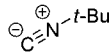
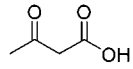
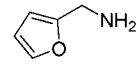
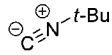
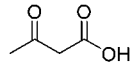
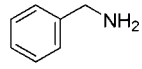
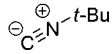
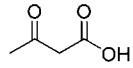
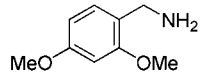
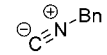
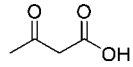
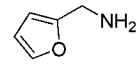
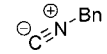
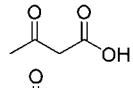
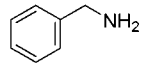
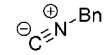
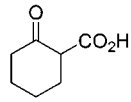
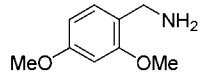
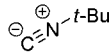
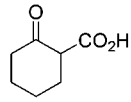
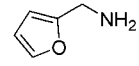
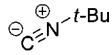
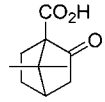
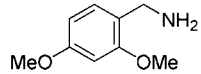
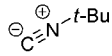
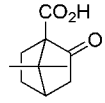
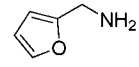
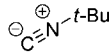
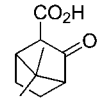
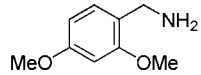
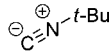
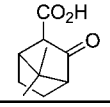
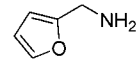
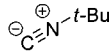


completion, whereas in MeOH several days are required; this fact is explained by an acceleration effect exerted by the water. This increase of rate occurs because the ring formation takes place with volume contraction in the transition state; therefore, this reaction is responsive to pressure and aqueous solution (Scheme 13).[27]

The accelerating effect of water over multicomponent reactions such as the Ugi reaction was applied in the synthesis of highly strained ring-fused β-lactams starting from β-keto acids. This reaction, which in organic solvents simply does not occur, was slightly accelerated when aqueous glucose was used as cosolvent. The condensation of β-keto acids with isonitriles and amines yielded the expected β-lactams in moderate to reasonable yields (Table 15).[127]

In a recent study, the formation of the four-membered heterocyclic structure was accomplished with notable efficiency via intramolecular C−H insertion of dirhodium(II) carbenoids generated from diazo-acetamides. Afonso et al. performed the cyclization of diazo-phosphoryl-acetamides in water in the presence of $Rh_2(OAc)_4$ yielding exclusively the β-lactam, whereas in the absence of the catalyst, only the alcohol was obtained; this result clearly indicates the existence of a metallocarbenoid species involved in the C−C bond formation (Scheme 14).[128] This methodology was extended with considerable success to other families of diazo-acetamides as shown in Table 16.[128]

Table 15

Entry	β-Keto acid	Amines	Isonitriles	Time (days)	Yield β-lactam (%)
1				3	75
2				3	66
3				3	70
4				3	50
5				3	55
6				3	51
7				6	45
8				6	49
9				6	16
10				6	21
11				6	31
12				6	31

Scheme 14

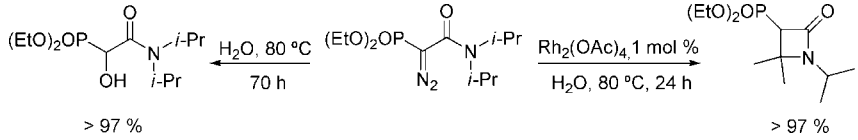
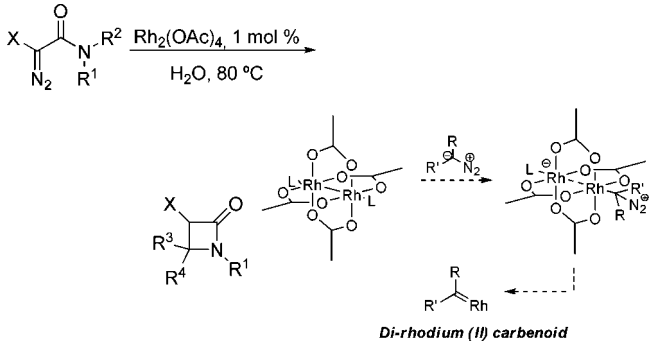
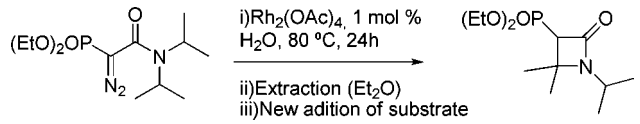


Table 16



entry	X	R^1	R^2	R^3	R^4	time (h)	ratio (*trans*/*cis*)	yield (%)
1	PhO_2S	*i*-Pr	*i*-Pr	Me	Me	21		73
2	MeO	*i*-Pr	*i*-Pr	Me	Me	24		>97
3	EtO_2C	*i*-Pr	*i*-Pr	Me	Me	24		76
4	EtO_2C	*t*-Bu	$PhCH_2$	Ph	H	24	1.3:1	>97

Table 17



run	average yield (%)	average Rh in Et_2O (%)
1−9	88	1.6
10	90	1.1
11	(63)[a]	0.2

[a] Observed conversion.

As pointed out in the Introduction, water in some cases allows a simple and efficient way to execute catalyst reutilization. The catalyst used in this procedure is water-soluble due to complexation of water in the $Rh_2(OAc)_4$ axial positions; this fact permitted catalyst reutilization over 11 cycles affording continuously high yields of β-lactam. Interestingly when the Rh content was determined by inductively coupled plasma (ICP) in the organic phase, it was verified that most of it remains in the aqueous phase; this fact clearly highlights the utility of this method (Table 17).[129]

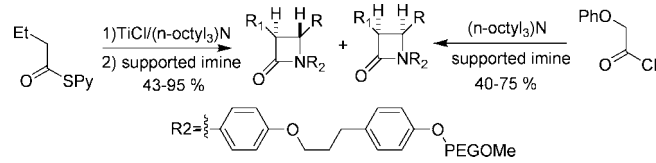
Further comments on this particular transformation will be given in section 4, where the synthesis of five-membered heterocycles is discussed.

3.3. Reactions in PEG or PEG Tag Approaches

In the four-membered heterocycle family, β-lactams attracted great attention due to their known application as antibiotics, penicillin derivatives. They could be prepared via a cycloaddition reaction between ketenes and imines or via condensation between imines and enolates from thioesters.

Cozzi et al. achieved for the first time the synthesis of supported β-lactams by preparing several imines attached to a soluble $MeOPEG_{5000}$ polymer matrix. Further studies demonstrated that the spacer plays an important role in the overall yield (imine immobilization, β-lactam formation, and support removal).[130,131] When 3-(4-hydroxyphenyl)-1-propanol was used as spacer, heteroaromatic, aromatic, unsaturated, and aliphatic imines were prepared and reacted with *in situ* generated ketenes and with thioesters in good to excellent yields (40−95% yields, Scheme 15). N-Unprotected β-lactam was then obtained by oxidative cleavage with CAN ($Ce(NH_4)_2(NO_3)_6$).

Scheme 15



Wang et al. reacted PEG-supported imines with ketene precursors with somewhat higher yields (65−99%) and high purities of up to 99% (Scheme 16, reaction 1).[132] An interesting alternative was explored by the same group, when the ketene precursor was immobilized in the PEG polymer.[133] In this case, since the reaction was run in presence of zinc powder the desired lactam is the only organic product dissolved in the solvent (Scheme 16, reaction 2).

3.4. Reactions in Ionic Liquids

Ionic liquids can be used to prepare four-membered rings such as β-lactams in good to moderate yields. Gois and Afonso[134] described the preparation of β- and α-lactams in high yields (≥71%) with high regio- and stereoselectivities via $Rh_2(OAc)_4$-catalyzed intramolecular C−H insertion in IL [bmim][PF_6] (Scheme 17). The use of dirhodium(II) tetraacetate catalyst in the formation of metal carbenes starting from diazo carbonyl compounds has been described as a useful carbon−carbon bond forming methodology, particularly using intramolecular carbon−hydrogen insertion reactions in the heterocyclic ring synthesis.[135−137]

The authors observed that the IL [bmim][PF_6] is an excellent medium for the immobilization of $Rh_2(OAc)_4$ catalyst and for providing the formation of five-member rings with preferential stereocontrol for the *trans* diastereomer, as well as using chlorinated solvents (Scheme 17).[138] The influence of the electron-withdrawing group directed the reaction toward the exclusive β-lactam formation. The catalytic system (IL/Rh catalyst) was recycled six times with high yields of product (71−93%) and high turnover number of the catalyst (TON = 493) using *n*-hexane and *tert*-butyl methyl ether as extracting solvents.

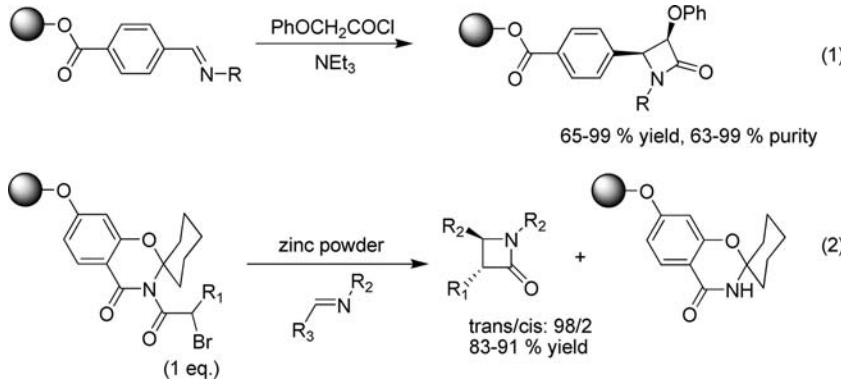
4. Five-Membered Rings

4.1. Containing One Nitrogen Atom

4.1.1. Solvent-Free Reactions

The preparation of pyrroles in SFC can be accomplished via the Paal−Knorr route. In the described examples (Table 18), performed under MWI, it was observed that the increase

Scheme 16



Scheme 17

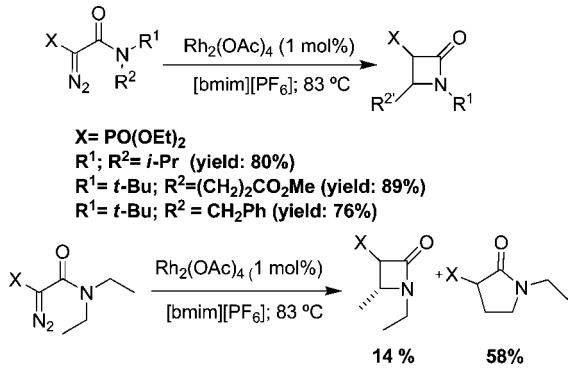
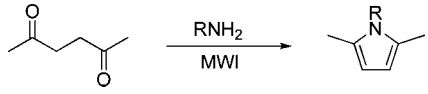


Table 18

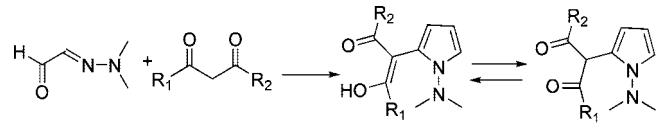


entry	R	yield (%)
1	$PhCH_2$-	90
2	$PHCH_2CH_2$-	90
3	Ph-	90
4	3-ClPh-	80
5	4-CH_3OPh-	90
6	2-CH_3Ph-	85
7	2,4-CH_3Ph-	80
8	2,6-CH_3Ph-	75

of the nucleophilic character of the amine led to high yields of the corresponding pyrroles in shorter reaction times and at lower power settings. On the other hand, 2-substituted aryl amines require longer reaction times and higher power because of stereochemical constraints.[139] Later, it was reported that the use of K-10 montmorillonite as catalyst improves the reaction, leading to the formation of the desired pyrroles in quantitative yields.[140]

Recently, potassium-exchanged layered zirconium phosphate (α-$Zr(KPO_4)_2$) and zirconium sulfophenyl phosphate (α-$Zr(CH_3PO_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$) were developed as catalysts for the solvent-free version of Paal−Knorr reaction. With these catalysts, high to moderate yields can be obtained at room temperature, except when amine substituent steric hindrance is present.[141] Analogously, the presence of 1 mol % scandium triflate in the Paal−Knorr solvent-free reaction is very effective toward formation of desired pyrroles.[142] These units can also be prepared in moderate yield from condensation of monodimethylhydrazone of glyoxal and dicarbonyl compounds in presence of a catalytic amount of piperidine at room temperature. However, this method can be less attractive because of the need for very long reaction

Table 19



entry	R_1	R_2	reaction time (days)	yield (%)	**a/b**
1	Me	OEt	6	60	42/58
2	Et	OMe	13	43	35/65
3	*i*-Pr	OEt	33	21	0/100
4	Me	Me	1	62	100/0

times (Table 19).[143] Similarly, an N-substituted pyrrolidine nucleus fused with a dihydrofuran backbone can be obtained by reaction of glyoxal monophenylhydrazones with β-ketoesters by conventional heating or through MWI.[144]

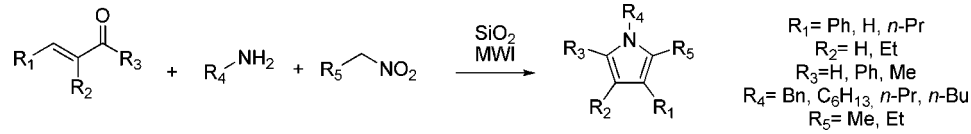
Two other methods developed for the preparation of pyrroles and fused pyrroles in solvent-free conditions consist of two distinct couplings under MWI in a domestic microwave oven. The first method is based on the coupling of an α,β-unsaturated aldehyde or ketone, an amine, and a nitroalkane on the surface of silica gel (Scheme 18),[145] which was recently modified through introduction of *N*,*N*-disubstituted thiobarbituric acids instead of α,β-unsaturated aldehyde, to afford pyrrolo[2,3-*d*]pyrimidines.[146] The second method is a coupling of a carbonyl compound, an amine, and an α,β-unsaturated nitroalkene on the surface of alumina (Scheme 19). In this last procedure, the nitroalkene α-substituent (R_3) seems to be essential since its absence takes the reaction along different pathways. It is also conditional that open chain carbonyl compounds are aldehydes, since the use of open chain ketones led to different reaction products.[145,147]

Recently, an asymmetric synthesis of pyrroles was achieved in good yields, by coupling chloroenones and chiral amines onto the surface of silica gel in presence of triethylamine and after irradiation with microwaves for less than 10 min.[148]

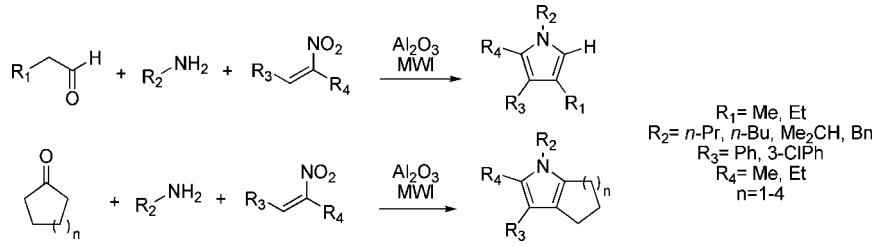
Pyrrole ethynylation can be performed in mild conditions through the coupling of 1-acyl-2-bromoacetylenes on the surface of alumina to afford 2-(acylethynyl)pyrroles in reasonable yields (55−70%) and excellent regioselectivity.[149]

Concerning the transformations of pyrrole N-substituent, a method for the phosphorylation of 1-isopropenylpyrroles is described as the reaction of this pyrrole with secondary phosphines at 65 °C in presence of AIBN. Despite the long reaction times (1−13 days), this solvent-free synthesis leads to the desired pyrroles in good yields (89−92%).[150] Recently, Prauda et al. reported the reaction of N-heterocycles (pyrrolidine, piperidine derivatives, morpholine, and piperazine

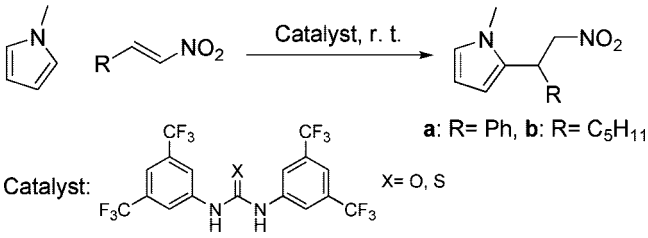
Scheme 18



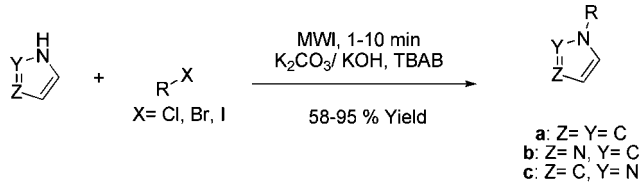
Scheme 19



Scheme 20



Scheme 21



derivatives) with paraformaldehyde and diethylphosphite or $Ph_2P(O)H$ to yield phosphono- and phosphinoxidomethylated N-heterocycles.[151]

Through Friedel−Crafts alkylation with nitroolefins in presence of an organic catalyst, alkyl substituents can be introduced in good yields at room temperature in the 1-position of the pyrrole ring (Scheme 20).[152] Similar to the phthalamide alkylation method described,[153] a selective method for the alkylation of the pyrrole nitrogen atom can be adopted using potassium hydroxide besides the mentioned potassium carbonate.[154] Furthermore, this method can be successfully applied to the modification of other heterocycles such as imidazole, pyrazole, indole, and carbazole (Scheme 21).

Pyrrole-based DPP pigments (3,6-diaryl-1,4-diketopyrrolopyrrol) can be prepared by MWI of ethylbromoacetate, arylnitrile, and zinc−copper for 10 min. Good to moderate yields are obtained when electron-donating *para*-substituted benzonitriles are used, while electron-withdrawing *para*-substituted benzonitrile and strong electron-donating groups lead to no reaction.[155]

The microwave-induced intramolecular 1,3-dipolar cycloaddition of azomethine ylides, by reaction of an aldehyde and an α-amino acid ester is useful in the synthesis of pyrrole derivatives hexahydrochromeno[4,3-*b*]pyrroles (Scheme 22); however, it should be noted that the reaction yield is very sensitive to the steric demands of the nitrogen atom substituent.[156,157]

The formation of pyrrolidines was seen to occur in a microwave oven through the 1,3-dipolar cycloaddition reaction of *in situ* generated azomethine ylides with 9-arylidene fluorenes. The azomethine ylides can be formed by decarboxylative condensation of ninhydrin and sarcosine or from reaction between isatin and secondary amino acids.[158,159]

The acid-catalyzed Mannich-type reaction between *N,O*-acetals and *β*-dicarbonyl compounds has proved to be a better method for the pyrrolidine substituent modification under SFC at room temperature than reaction in dichloromethane (Table 20).[160] Recently, $InCl_3$ was reported as being an excellent catalyst for this room-temperature transformation (83−94% yield) and also for the introduction of activated olefins containing a trimethylsilyloxyl moiety in *N*-Boc-2-methoxypyrrolidine or in the six-membered homologue.[161] On the other hand, an N-substituent can be introduced in pyrrolidine or in piperidine in good yields by reacting it with 2- or 4-halopyridine under microwave irradiation[162] and

Scheme 22

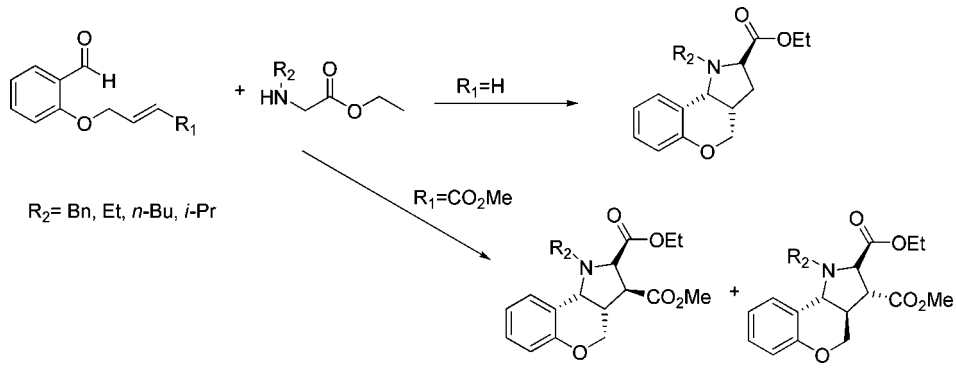
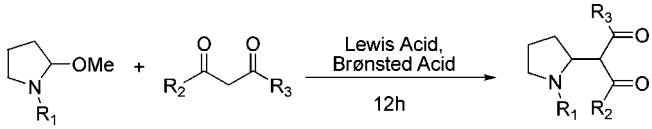
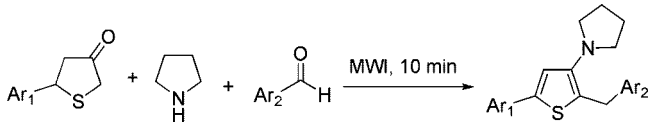


Table 20



entry	R_1	R_2	R_3	acid	yield (%)
1	CO_2Me	Me	Me	*p*-TsOH	94
2	CO_2Me	Me	OMe	CF_3SO_3H	93
3	CO_2Me	OMe	OMe	$TiCl_4$	76
4	CO_2Me	Me	Ph	*p*-TsOH	77
5	CO_2Me	Ph	Ph	*p*-TsOH	63
6	CO_2Me	cyclohexan-1,3-dione		*p*-TsOH	83
7	CO_2CH_2Ph	Me	Me	*p*-TsOH	82
8	CO_2CH_2Ph	Me	OMe	*p*-TsOH	78
9	CO_2CH_2Ph	Ph	Ph	*p*-TsOH	81

Table 21



entry	Ar_1	Ar_2	yield (%)
1	4-ClC_6H_4	4-MeC_6H_4	60
2	4-MeC_6H_4	2,4-$Cl_2C_6H_4$	53
3	4-MeC_6H_4	3-FC_6H_4	46
4	4-ClC_6H_4	4-FC_6H_4	45
5	3-$NO_2C_6H_4$	4-ClC_6H_4	60
6	2,4-$Cl_2C_6H_4$	4-ClC_6H_4	57
7	3- $NO_2C_6H_4$	1-$C_{10}H_7$	53

enamines can be obtained by reaction of cyclic amines such as pyrrolidine, morpholine, or piperidine with a ketone under MWI in presence of K-10 clay[163] or Envirocat EPZG^R.[164]

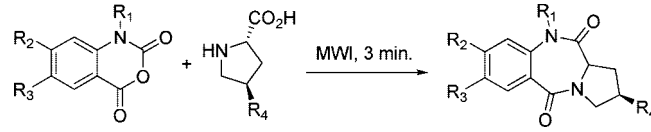
Through the use of microwave irradiation, thienylpyrrolidines can be obtained by condensation of pyrrolidine with 5-aryldihydro-3(2*H*)-thiophenone in presence of an aromatic aldehyde (Table 21). After enamine formation, carbonyl addition occurs and aromatization of the sulfur heterocyle yields the final product in reasonable yields (45−60%). When piperidine was used as the amine, lower yields were observed (30−35%).[165]

Phthalamides are another heterocyclic class of compounds that can be seen as a simple skeleton, since they can be alkylated under microwave irradiation under SFC using an alkyl halide in 25% excess, tetrabutylammonium bromide in a catalytic amount, and the reactants immobilized in potassium carbonate. Good to excellent yields can be obtained in 4 min, and it should be noted that instead of the phtalamide potassium salt, the reaction is performed using commercial phthalamide.[153] This procedure can also be efficiently adopted for the N-alkylation of carbazole taking in consideration the longer reaction times (4−10 min).[166]

An efficient procedure for the synthesis of highly valuable pyrrolo[2,1-*c*][1,4]benzodiazepines has been developed through the use of microwave irradiation of isatoic anhydride and L-proline derivatives in a few minutes (Table 22).[167]

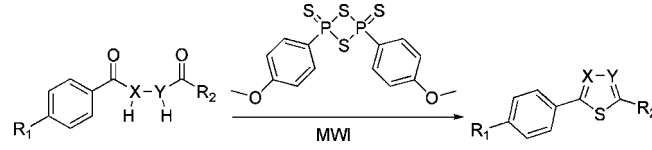
For the preparation of 2-substituted thiophenes (Table 23, entries 1−9), an efficient procedure through the use of MWI has been developed. This procedure consists of Lawesson's reagent mediated cyclization of 1,4-dicarbonyl compounds in a conventional microwave oven (Table 23). Depending on the 1,4-dicarbonyl compounds used, 1,3-thiazoles (Table 23, entry 10) and alkylthiadiazoles (Table 23, entry 11) can also be obtained; however special care should be taken on

Table 22



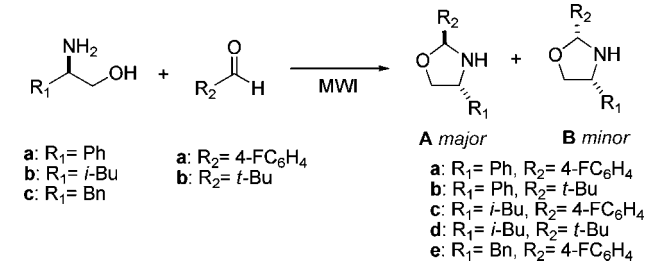
entry	R_1	R_2	R_3	R_4	yield
1	H	H	H	H	81
2	H	H	H	OH	80
3	H	H	Me	H	92
4	H	H	Me	OH	90
5	H	OH	MeO	H	82
6	H	OH	MeO	OH	80
7	Me	H	H	H	90
8	Me	H	H	OH	86

Table 23



entry	R_1	X	Y	R_2	time (min)	yield (%)
1	Br	CH	CH	C_2H_5O	3	90
2	Br	CH	CH	*n*-C_4H_9O	3	89
3	Br	CH	CH	*n*-$C_6H_{13}O$	3	94
4	Br	CH	CH	*n*-$C_6H_{17}O$	3	89
5	Br	CH	CH	$C_6H_{13}OCH(CH_3)O$	3	89
6	Br	CH	CH	*n*-$C_{10}H_{21}O$	3	93
7	Br	CH	CH	*n*-$C_{12}H_{25}O$	3	87
8	MeO	CH	CH	4-BrC_6H_4O	3	65
9	H	CH	CH	Ph	4	92
10	Br	N	CH	*n*-$C_{12}H_{25}O$	5	90
11	Br	N	N	*n*-$C_{13}H_{27}$	7	95

Scheme 23

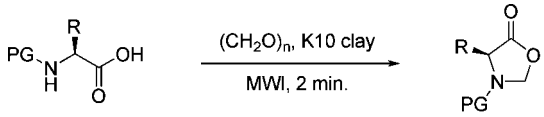


the irradiation times since overexposure of the reaction products to the microwaves leads to decreased yield.[168]

The reaction of activated nitriles and α-mercaptoesters under MWI led to the formation of *β*-enamino-type (*Z*)-4-oxothiazolidine derivatives in presence of a catalytic amount of potassium carbonate.[169]

1,3-Oxazolidines can be obtained in excellent diastereoselectivities and good yields by reaction between an amino alcohol and an aldehyde under microwave irradiation for a few seconds. The use of equimolar amounts of reactants and the equilibrium shift toward the more thermodinamically stable diasteroisomer **A** makes it possible to obtain oxazolidine in good purity without further purification (Scheme 23).[170] Similarly, 2-oxazolines can be obtained by direct condensation of carboxylic acids with amino alcohols, since the high temperature induced by microwaves ($T > 150$ °C) makes this step irreversible by water removal. In this procedure, the presence of two hydroxyl groups seems to be crucial; however when this second hydroxyl is absent, a

Scheme 24



PG= Ts, MeCO, PhCO;
R= CH_3, *i*-Pr, $(CH_3)_2CHCH_2$, Bn, $CH_3CH_2CH(CH_3)$, $BnOC_6H_4CH_2$

catalyst like zinc oxide can be added to catalyze the reaction.[171,172]

With the use of microwave-induced 1,3-dipolar cycloaddition of 2-aroyl-aziridines with 4-nitro benzaldehyde as dipolarophile, the corresponding 1,3-oxazolidine can be obtained in 80% yield in 15 min.[173] Furthermore, depending on the dipolarophile used, several heterocyclic systems can be obtained, like imidazolidines, oxazoles, and pyrrolines. Similarly, the microwave induced 1,3-dipolar cycloaddition of conjugated nitrones with unactivated alkenes can also be used to obtain isoxazolidines.[174]

Another way to synthesize 2-oxazolines was described as the 1,3-dipolar cycloaddition between an imidate and several aldehydes. This procedure can be performed under MWI or by conventional heating, yielding the 2-oxazoline in good yields and moderate diastereoisomeric rates (when applicable).[175,176] Through the use of microwaves, tricyclic isoxazolidines fused with a pyrroline or piperidine ring can be obtained in good yields by an intramolecular oxime−olefin cycloaddition in the presence of silica gel[177] and *N*-(benzylidene)methylamine *N*-oxide can react with α-trifluoromethylstyrene by 1,3-dipolar cycloaddition to afford the corresponding isoxazolidine in 94% yield without the use of any inorganic support.[178]

Through the MWI of N-protected amino acids in presence of paraformaldehyde and K-10 clay, N-protected oxazolidine-5-ones can be obtained in good to excellent yields (91−96%) in a couple of minutes when tosyl, acetyl, and benzoyl are used as the protecting groups (Scheme 24). Despite the simplicity and efficiency of this protocol, it should be noted that the use of Boc and Cbz should be avoided since they lead to a complex mixture of products due to decomposition.[179]

Using palladium(II) acetate, one can obtain 2-phenyl-5(4*H*)-oxazolones by reaction of the appropriate aldehyde or ketone with hippuric acid. Despite the use of microwaves leading to higher yields (51−98%), conventional heating can also be used, and the correspondent oxazolones are obtained in satisfactory yields (41−83%).[180] Recently, diammonium hydrogen phosphate was used as catalyst in the formation of these azlactones (82−92% yield) through the reaction of hippuric acid with an aldehyde and acetic anhydride at 80 °C.[181] Ytterbium(III) triflate was reported as a suitable catalyst for the same reaction in milder conditions. The solvent-free reaction at 40 °C was tested with several metal triflates, and the optimum conditions were determined using 10 mol % of $Yb(OTf)_3$ regardless of the benzaldehyde substituent electronic effect.[182] About the substituent modification, 2-phenyl-5(4*H*)-oxazolones were reported to react with aliphatic aldehydes upon adsorption on neutral alumina and after microwave exposure to give the product with an exocyclic double bond in the 4-position of the ring in good yields (62−78%).[183]

Oxazoles can be prepared by microwave irradiation of amides or nitriles with intermediary α-ODNs-substituted ketone, formed *in situ* by reaction of hypervalent iodine(III) sulfonate with ketones (Scheme 25),[184,185] and hydroxyacetophenone oxime led to the formation of 2-methyl benzoxazole through the microwave-induced, $ZnCl_2$-mediated Beckmann rearrangement.[186]

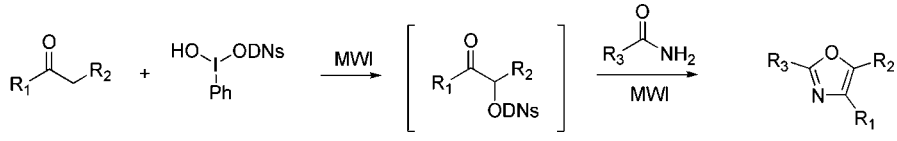
Isoxazoles can be obtained under MWI in dry media by 1,3-dipolar cycloaddition of *in situ* generated arylnitrile oxides and a dipolarophile. The formation of the oxide species is facilitated by the presence of an oxime and NCS in the reaction medium (Scheme 26).[187−189] By use of an alkene as dipolarophile, this method proved also to be efficient in the preparation of isoxazolines.[188] Recently, a one-pot procedure was reported for this reaction in which the reaction between Oxone, acidic silica gel, and an aldoxime at room temperature for 13 min led to the formation of halogenated aldoxime and is further reacted with triethylamine and styrene for 2 min.[190]

Through the combined use of one-pot Knoevenagel and Michael reactions between rhodanines, aromatic aldehydes and ammonium *N*-aryl-dithiocarbamates, the dithioesters formed can be cyclized to furnish thiazolo-1,3-dithiins, -thiazines, or -oxathiins depending on the inorganic species used (Scheme 27). For the annulation of formed dithioesters, montmorillonite K-10 clay, modified Li^+-montmorillonite clay, and molecular iodine were used to yield different families of compounds under microwave irradiation (77−89% yield). The use of classic thermal conditions proved to be less effective, resulting in the formation of the same compounds in lower yields (42−52%).[191]

A simple procedure for the preparation of thiazoles has been described. Under SFC, a thioamide is mixed with α-tosyloxyketones and montmorillonite K-10 clay and then submitted to microwave irradiation for a few minutes, resulting in the desired thiazoles in good yields (Scheme 28). This procedure can also be expanded to the synthesis of the corresponding bridgehead heterocycles using cyclic ethylene thiourea.[192] As already described for the preparation of benzimidazoles, the synthesis of benzothiazoles can be performed in a microwave oven by condensation of 2-aminothiophenol with *in situ* generated chlorides of hydroxamic acids in presence of alumina.[193]

A solid state based procedure for the preparation of thiazoles has been recently reported. This procedure consists of ball-milling α-haloketones with arylidenethiosemicarbazone derivatives to form the corresponding iminium salts with water evaporation at 80 °C in vacuum. The simple wash

Scheme 25

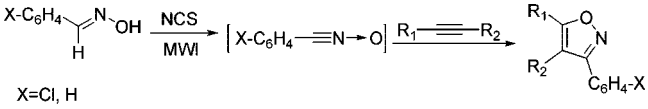


R_1=Ph, Me, 4-MeC_6H_4, 4-ClC_6H_4
R_2= H, Me, COMe, CO_2Et, $CONEt_2$, Ph

R_3= Me, Ph

DNs=2,4-dinitrobenzenesulfonyl

Scheme 26



of the salt with aqueous Na_2CO_3 easily liberates the desired thiazoles in quantitative yields.[194]

Thiazole derivatives, iminothiazolines, can be achieved by the reaction between a thiourea and α-chloroketone under MWI at 80 °C in presence of alumina; however in the absence of alumina, iminothiazolines hydrochloride salts are formed. In both of these procedures, the reaction yield is greatly improved compared with conventional heating.[195] Recently, 2-acylimino-3-aryl-3*H*-thiazolines were prepared through reaction of arylisothiacyanates, generated from reaction of acyl chloride and potassium thiocyanate, with an aniline derivative and an α-haloacetophenone (Table 24). Despite the good yields obtained in the microwave version of this reaction, the same products could be obtained in reasonable yields under conventional heating conditions (1 h at 80 °C). Despite the absence of a substituent effect on the acyl moiety, only donating substituents in the aniline derivatives were seen to be suitable for the reaction to occur.[196]

Similar to the reported one-pot synthesis of iminothiazoline derivatives,[195] 5-arylidene-2-imino-4-thiazolidinones can be obtained by microwave-induced condensation of a thiourea, chloroacetic acid, and an appropriate aldehyde.[197] Through MWI, 2-hydrazinothiazolon-5-one can be obtained in 89% yield by reacting thiosemicarbazide with chloroacetic acid[198] and 2-amino-5-arylidene-1,3-thiazol-4(5*H*)-ones through the Knoevenagel reaction of rhodanine derivatives, aryl aldehyde, and an *n*-propyl amine and further reaction with a cyclic amine by sulfur/nitrogen displacement (Scheme 29).[199] 4-Oxo-thiazolin-5-ylidene was recently prepared under MWI through the reaction between dimethyl acetylene dicarboxylate (DMAD) and thiosemicarbazone derivatives. After 5 min irradiation, good to excellent yields were reached (82−95%).[200] The introduction of N-alkyl substituents in the thiazole ring system can be performed in the same way that N-alkyl substituents are introduced in imidazole to prepare imidazolium ionic liquids.[201]

4.1.2. Reactions in Aqueous Media

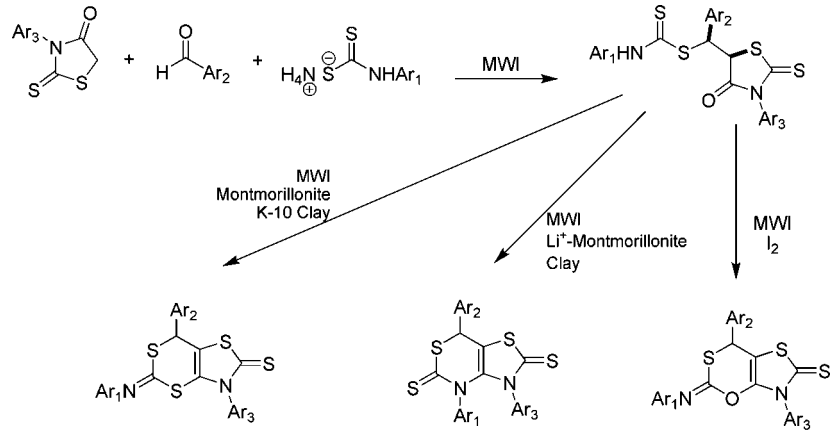
The synthesis of pyrrole and indole derivatives has also been attempted in aqueous media, most of the reported methodologies deal with their alkylation. Among these, the work of Jørgensen et al. is particularly noteworthy. This group reported the Lewis/Brønsted acid free Friedel−Crafts reaction of carbonyl compounds with heteroaromatic compounds in water. The Friedel−Crafts reaction proceeds well for pyrroles in water. Methyl pyrrole reacts with ethyl glyoxylate in a saturated solution of $NaHCO_3$ to give the 2-alkylated product in 87% yield (Scheme 30).[202]

Hashemi et al. reported on a new one-pot method to prepare substituted 4-hydroxy pyrroles. The three-component reaction of *β*-dicarbonyl compounds with arylglyoxals in the presence of ammonium acetate in water at room temperature afforded the desired products in poor to excellent yields (Scheme 31).[203] Yavari et al. also reported on the synthesis of pyrroles resulting from a rather complex reaction between 3,4-diacetylhexane-2,5-dione and primary amines in refluxing water (Table 25).[204]

Taking advantage of recent advances in the area of aqueous acid catalysis and its application to dehydrative esterification reactions,[205] Shinokubo, Osuka, et al. were successful in the preparation of novel expanded porphyrins (porphyrin analogues with more than four pyrrolic subunits).[206] These heptaphyrins were obtained via the condensation catalyzed by $Sc(OTf)_3$ of pyrrole with pentafluorobenzaldehyde in an aqueous micellar system followed by oxidation with DDQ in dichloromethane (Scheme 32).

The five-membered heterocyclic structures are widely present as motifs in an assortment of biologically active molecules. Azasugars, or polyhydroxylated N-heterocycles, are examples of such molecules, which exhibit pharmacologically relevant activity as a glycosidase inhibitor. Lindström et al. reported the asymmetric total synthesis of azasugars in water.[207] The preparation of a pyrrolidine azasugar was achieved in four high yield steps (Scheme 33). The key catalyzed transformation involved the Sharpeless asymmetric dihydroxylation of 1,6-dibromodiene (in 70% yield and 97% ee), with selective hydrolysis at the allylic position. Finally, highly diastereoselective epoxidation (99% yield and 92% diastereoselecivity) with a dinuclear peroxo-

Scheme 27



a: Ar_1= Ph, Ar_2= 4-ClC_6H_4
b: Ar_1= Ph, Ar_2= 4-$MeOC_6H_4$
c: Ar_1= 2-MeC_6H_4, Ar_2= Ph
d: Ar_1= 2-MeC_6H_4, Ar_2= 4-ClC_6H_4
e: Ar_1= 2-MeC_6H_4, Ar_2= 4-$MeOC_6H_4$

Scheme 28

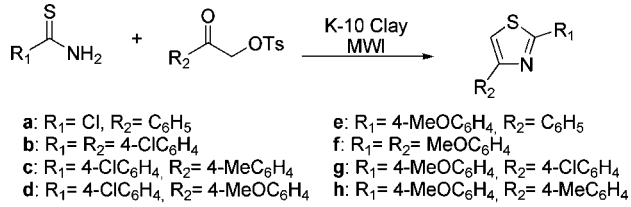
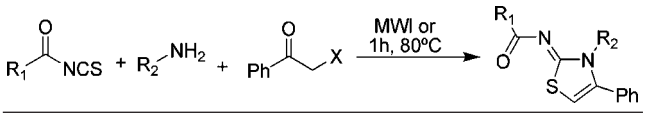


Table 24



entry	R_1	R_2	conventional heating yield (%)	MWI reaction time (s)	MWI yield (%)
1	Ph	Ph	72	30	90
2	Ph	2-MeC_6H_4	77	30	93
3	Ph	4-MeC_6H_4		30	98
4	Ph	4-ClC_6H_4	62	45	90
5	Ph	4-$MeOC_6H_4$	41	30	87
6	4-ClC_6H_4	2-MeC_6H_4		45	88
7	4-ClC_6H_4	4-MeC_6H_4	66	30	84
8	4-$MeOC_6H_4$	4-ClC_6H_4	71	45	96
9	4-$MeOC_6H_4$	4-$MeOC_6H_4$		30	91
10	4-$NO_2C_6H_4$	4-ClC_6H_4		30	89
11	Ph	3-ClC_6H_4	69	45	83

tungstate catalyst, selective for epoxidation of allylic alcohols in water and ammonia, promoted ring closure, affording the azasugar in 60% overall yield (Scheme 33).[207]

Recently Varma et al. reported a straight forward methodology to prepare a variety of four, five, six, and seven heterocyclic units. This was accomplished through a double alkylation of several aniline derivatives by alkyl dihalides. This reaction takes place in mildly basic aqueous solution upon microwave irradiation providing the desired products in moderate to high yields (Table 26).[208] The microwave irradiation as a particular important accelerating effect for this transformation because it achieves excellent product yields in just 20 min whereas under conventional heating conditions only 58% yield is obtained for the same reaction after 8 h.[208]

Morimoto, Kakiuchi, et al. disclosed a manuscript in which a catalytic Pauson−Khand-type reaction of enynes in aqueous media allows the preparation of a variety of cyclic and heterocyclic compounds. As a distinctive feature, this transformation uses formaldehyde as a substitute for the dangerous carbon monoxide gas.[209] This transformation involves two distinct steps and both take place simultaneously in a different reaction field. The rhodium-catalyzed decarboxylation of formaldehyde occurs in the aqueous phase whereas the carbonylation takes place in the micellar phase. The authors presented the hypothesis in Scheme 34 to rationalize the experimental evidence.[209]

This Pauson−Khand-type reaction was applied in the synthesis of *N*-tosyl pyrrolidines with considerable success, using SDS as the surfactant and 1,3-bis(diphenylphosphino)propane (dppp)/3,3′,3″-phosphinidynetris(benzenesulfonic acid) trisodium salt (TPPTS) as the ligand system (Table 27).[209]

A detailed study on the cyclization of diazo-acetamides in water catalyzed by dirhodium(II) complexes was presented by Afonso et al. The preparation of γ-lactams via intramolecular C−H insertion of diazo-acetamides was shown to be dependant on the catalyst used and the substrate structure. In close agreement with the concept of "on water" reactions, it was observed in this study that substrates with higher solubility in water yielded considerably more alcohol than those substrates that formed droplets of bulk diazo in the aqueous phase (Table 28).[128,129] The catalyst hydrophobic nature clearly influences the cyclization process; in both examples, the more hydrophobic $Rh_2(Ooct)_4$ directs the insertion toward γ-lactam formation. This fact indicates that $Rh_2(Ooct)_4$ increases the metallocarbenoid hydrophobic nature, and for this reason, the reaction proceeds without the presence of water near the carbene center.[128,129]

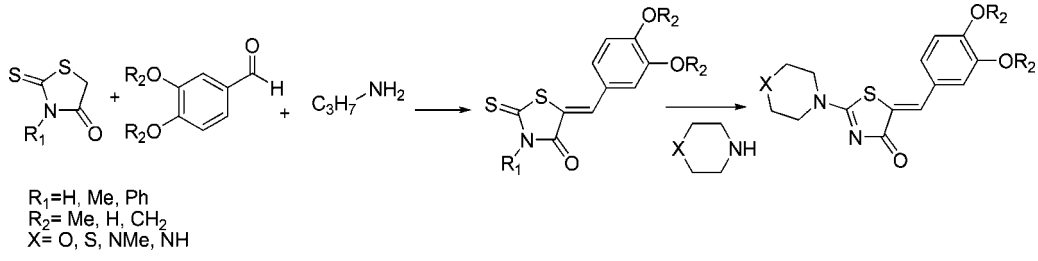
The synthesis of γ-lactams has been reported in water via a radical protocol using water-soluble radical initiators **A** and **B**. These radical initiators were highly effective for the atom transfer cyclization of *N*,*N*-diallyl-2-iodoacetamide in water. Stirring for 1 h a mixture of substrate and **A** or **B** in water at 75 °C afforded the desired γ-lactam in 80% or 99% yield, respectively (Scheme 35).[210]

Recognizing the potential of radical methodologies to prepare highly functionalized cyclic compounds, Naito et al. reported a tandem C−C bond-forming reaction that proceeds smoothly in water to yield γ-lactams. An interesting feature of this transformation is the construction of a two C−C bonds via a tandem process (Scheme 36).[211,212] The cyclization of an oxime ether afforded the lactam in 63% yield as a diasteriomeric mixture enriched in the *trans* isomer. The rationalization presented by the authors for this tandem reaction involves alkyl radical addition to the oxime ether to form a carbonyl-stabilized radical. Subsequent intramolecular 5-*exo*-trig radical cyclization, favored by the oxime ether group, which acts as the acceptor group, yields the desired products. The preferential formation of the *trans* isomer is explained in terms of steric repulsion between the radical moiety and the oxime ether group.[211,212]

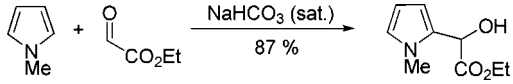
The reaction in water provided an important piece of evidence for a mechanism not involving the formation of the water-unstable boryl enolate (BE).

Olefin metathesis is a powerful methodology that enables C−C bond formation and is generally performed in organic solvents; with the intention of extending the scope of this transformation to aqueous solvents, Raines et al., developed new ruthenium complexes tuned in their electronic and steric environment. Combining N-heterocyclic carbene and sali-

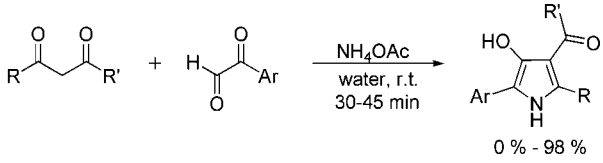
Scheme 29



Scheme 30

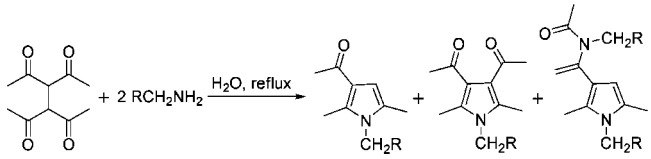


Scheme 31



R = Me, n-Pr
R' = Me, OMe, OEt, Ot-Bu
Ar = C_6H_5, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-PhC_6H_4, 4-$MeOC_6H_4$

Table 25



		yield (%)		
entry	R	ketone	diketone	amide
1	C_6H_5	71	10	14
2	4-Me-C_6H_4	81	14	12
3	4-OMe-C_6H_4	81	12	17
4	1-naphthyl	60	10	
5	4−Cl-C_6H_4	80	12	7
6	2−Cl-C_6H_4	79	8	5
7	Me	82	10	4

cylaldimine ligands allowed the efficient ring-closing methatesis of enynes in methanol/water mixtures (Scheme 37).[213]

4.1.3. Reactions in PEG or PEG Tags Approaches

Rao and co-workers tested for the first time the application of PEG_{200} as solvent for microwave-assisted (MW) reactions.[214,215] This polymer proved to be a suitable solvent media for palladium-assisted transfer hydrogenation and Paal−Knorr reaction (Scheme 38). Various aryl-substituted pyrrole derivatives were prepared in high yields within 1−5 min from enediones or ynediones and ammonium or akylammonium formates. This procedure furnished higher yields compared with the same reaction run in refluxing methanol.

Several protocols were described in the past since the pioneering work of Gewald et al. for the preparation of substituted 2-amino-thiophenes. But under homogeneous conditions, the condensation step involved presents two limitations: it requires long reaction times and difficult product purification. Those limitations prompted Yang and co-workers to develop a competitive method for Gewald synthesis, where cyanoacetic ester was immobilized in a soluble polymer matrix, PEG_{3400} (Scheme 39).[216] This polymer-supported reactant was then reacted in the presence of elemental sulfur, diisopropyldiethylamine (DIPEA), and various aldehydes, ketones, and 1,3-dicarbonyl compounds under solvent-free conditions in a microwave oven in which good to excellent yields were obtained. Application of microwave technology allowed the reduction of reaction time to 15 min, and the fact that the product at the end of the reaction is linked to the polymer offers an easy method for product purification by polymer precipitation with diethyl ether.

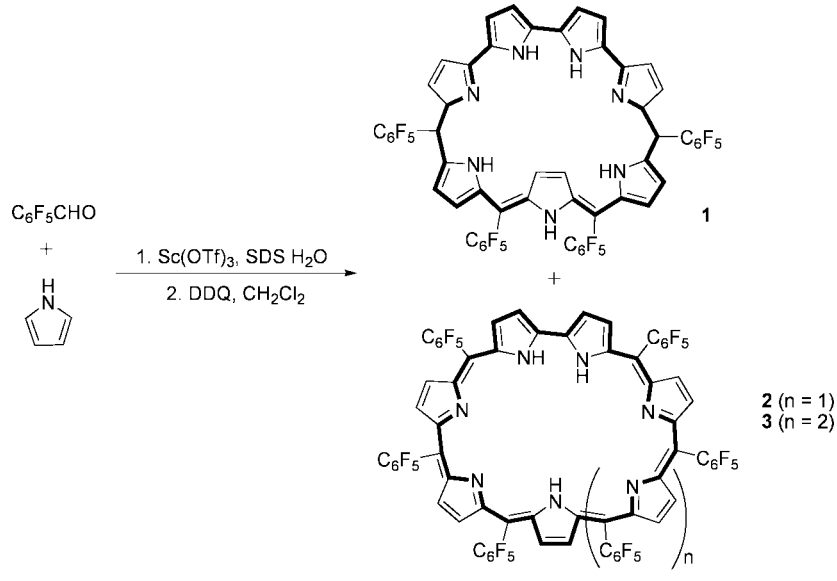
Yao demonstrated that a metathesis ruthenium catalyst could be attached to a soluble polymer, like PEG_{5000}, via a succinic moiety and used efficiently to prepare dihydropyrrole in excellent yield (Scheme 40).[217]

Wipf et al. developed an oxidant- and moisture-tolerant Burgess reagent by simply attaching it to a PEG polymer (MW = 2000). This dehydrating agent was successfully applied for the preparation of oxazolines and thiazolines (Scheme 41).[218]

The reaction afforded the desired heterocycle in higher yields (76−98%) compared with the original Burgess reagent (>78% yield) due to its enhanced stability. A few years later Manta et al. used this new dehydrating agent to prepare a thiazoline intermediate.[219]

Isoxazoles and isoxazolines are versatile scaffolds for the synthesis of a wide variety of complex natural products and are important pharmacophores in medicinal chemistry. These heterocycles could be synthesized by a 1,3-dipolar cycloaddition between the respectives alkynes or alkenes with nitrile oxides. Wang et al. explored the possibility to immobilize both alkynes and alkenes in soluble PEG polymers (MW = 4000) to quickly obtain a library of such desired molecules (Scheme 42). The nitrile oxide was prepared *in situ* by

Scheme 32



Scheme 33

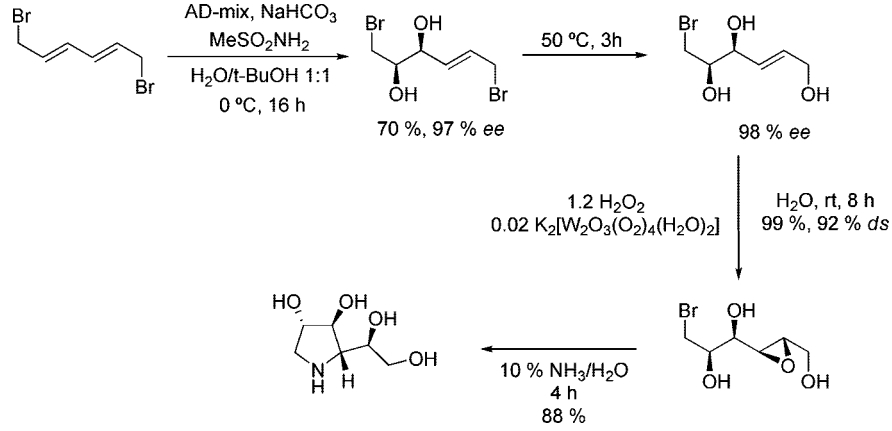
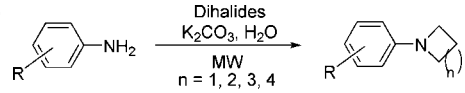
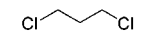
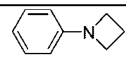
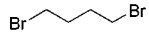
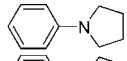
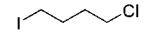
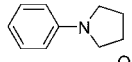
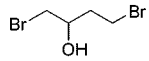
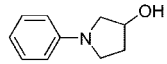
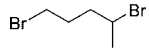
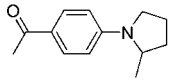
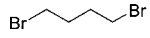
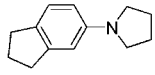
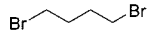
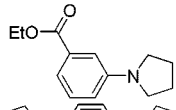
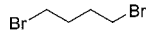
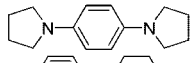
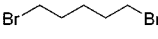
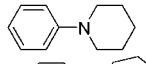
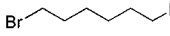
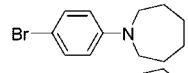
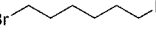
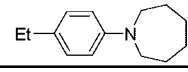


Table 26



Entry	R	Dihalides	Product	Yield (%)
1	4-H			54
2	4-H			89
3	4-H			76
4	4-H			42
5	4-CH_3CO			70
6	3,4-$(CH_2)_3$			96
7	3-EtOCO			93
8	4-NH_2			95
9	4-H			96
10	4-Br			65
11	4-CH_3CH_2			87

reacting aldoximes with NCS. Both heterocyclic compounds were prepared in good yields and excellent purity (>95%).[220]

Mantellini and Fillippone focused their efforts on preparing thiazolin-4-ones having an exocyclic 1,2-diaza-1,3-butadiene moiety. This was achieved by condensation of thioamides with PEG-supported 1,2-diaza-1,3-butadiene. The acyclic intermediary formed readily cyclized, eliminating the PEG support, to furnish the desired heterocycle in excellent purity (>91%), though in moderate yields (31−70%) (Scheme 43).[221]

4.1.4. Reactions in Ionic Liquids

The pyrrole ring constitutes a basic heteroatomic structure being a vital building block for the preparation of porphyrins and a key unit in a number of biologically active compounds.[222,223] The synthesis of alkylated pyrroles is normally problematic, since mixtures of regioisomers are formed from nonstabilized enamine intermediates.

Ranu et al.[224] reported a simple and green methodology for the synthesis of pyrroles through a one-pot condensation of carbonyl compounds (aldehydes or ketones), amines, and conjugated nitroalkenes in molten salt, tetrabutylammonium bromide, as a good media and catalyst, which does not require any other reagent or organic solvent (Table 29). By this procedure, a wide range of aldehydes and cyclic ketones were coupled with variety of primary amines and unsaturated nitroalkenes providing the corresponding substituted pyrroles. However, open-chain ketones do not lead to pyrroles by this procedure; instead the reaction stops at the intermediate imine product.

In the case of use of cyclic ketones instead of aldehydes, the corresponding fused pyrroles have been prepared in moderate to high yields as described (Table 30).

This alternative procedure offers significant advantages with regards to yield of products, reaction times, simplicity of operation, and more importantly recyclability and nontoxicity of the reaction medium selected.

Recently, Paal−Knorr condensation has been described as an efficient synthetic process for the preparation of pyrroles, pyrazoles, and their derivatives. In conventional conditions, an excess amount of several acidic materials such as zeolite,[225,226] Al_2O_3,[227] *p*-TSA,[228,229] $Ti(OPr^i)_4$,[230] and hazard organic solvents is used. More recently, Paal−Knorr condensation of 2,5-hexanedione with primary amines was successfully carried out in ionic liquids (Table 31).[231] In conventional systems, an excess of amine is required in order to promote the condensation.[141] In contrast, performing the reaction using ionic liquids such as [bmim][I], [bmim][BF_4], or [bmim][PF_6] allowed a simple product isolation procedure, high yields, exclusive selectivity, and accelerated reaction rates. Another important advantage is the recovery and reuse of ionic liquids three times without losing activity. The authors tested this methodology for several aliphatic and aromatic amines using optimized reaction conditions.[231] The aliphatic amines gave higher yields and shorter reaction times than are generally observed in other systems.

In the same line, Yadav et al.[232] described the immobilization of $Bi(OTf)_3$ in IL [bmim][BF_4] as a novel and reusable catalytic system for the synthesis of pyrrole derivatives from 1,4-diketones. The reactions were complete within 5 h, and the products were easily isolated by simple extraction with diethyl ether. Additionally, the remaining IL containing the catalyst could be recovered and recycled in successive reactions. The authors described the use of 5 mol % bismuth triflate/[bmim][BF_4] as the ideal catalytic system for these condensations. N-Substituted pyrroles are usually prepared

Scheme 34

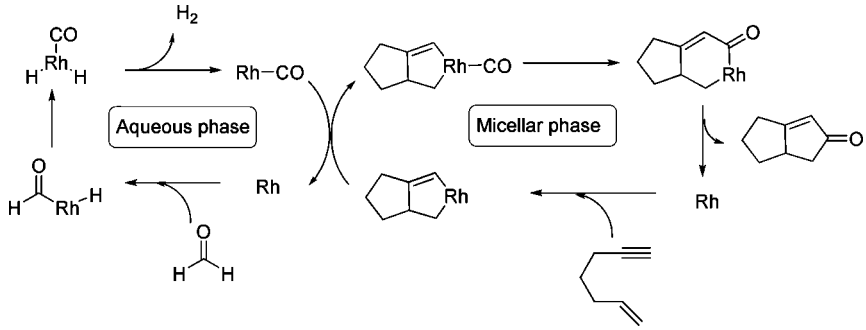
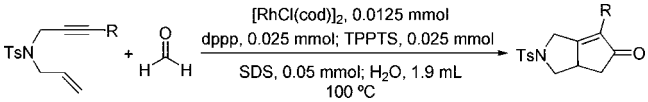
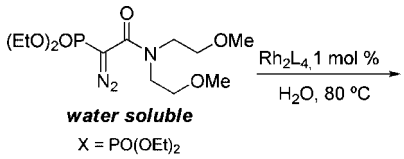


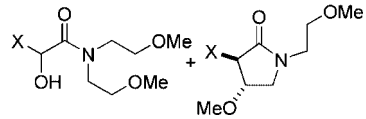
Table 27



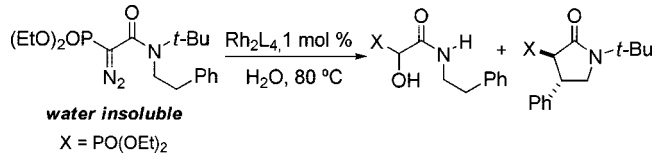
entry	R	reaction time (h)	yield (%)
1	Ph	2	96
2	Bu	6	89

Table 28





entry	time (h)	catalyst	yield (%)	α-hydroxyacetamide/ γ-lactam
1	48	$Rh_2(OAc)_4$	71	only α-hydroxyacetamide
2	24	$Rh_2(Ooct)_4$	62	1:0.46

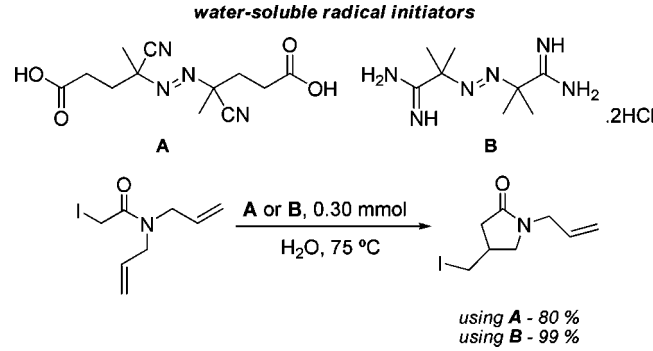


entry	time (h)	catalyst	yield (%)	α-hydroxyacetamide/ γ-lactam
1	48	$Rh_2(OAc)_4$	86	2.4:1
2	24	$Rh_2(Ooct)_4$	76	only γ-lactam

by the reaction of pyrrolyl anion with the appropriate alkylating agents.[233,234] When the anion from pyrroles is alkylated, the corresponding product N-alkylpyrrole may be contaminated with 2- and 3-alkylpyrroles.[235] N-Substitution of pyrrole can effectively be performed in the ionic liquids [bmim][PF_6] or [bmim][BF_4] with high regioselectivity, which provides a simple and efficient method for the synthesis of the N-substituted pyrroles as described in Table 32.[236]

The authors found that in the presence of KOH the reaction of pyrrole with methyl iodide could proceed at 40 °C in IL [bmim][PF_6].[236] This reaction is applicable to primary alkyl halides containing iodide, bromide, and chloride. In the case of secondary bromide, the yield is moderate (70%). This methodology was tested with several electrophilic olefins such as acrylonitrile, methyl acrylate, and methyl vinyl

Scheme 35



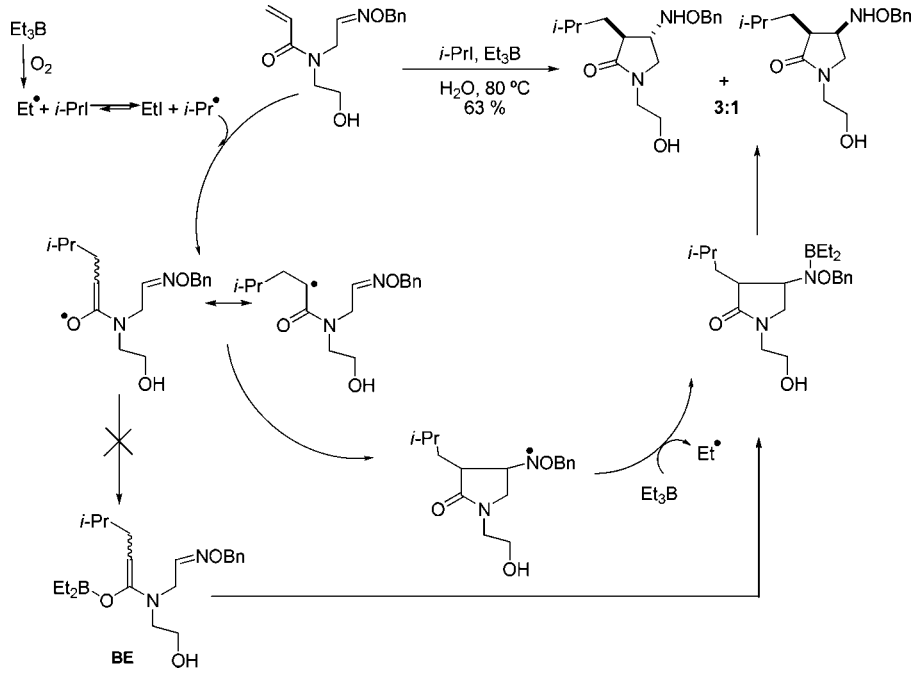
ketone and aromatic halides such as benzenesulfonyl chloride, benzoyl chloride, and *p*-methylbenzenesulfonyl chloride gave the corresponding N-substituted pyrrole derivatives in high to quantitative yields. *N*-Butylpyrrole was prepared in high yields using [bmim][PF_6] (98%) or [bmim][BF_4] (95%) as medium in the presence of KOH at 80 °C for 1 h. The ionic liquid could be recovered and reused after extraction of the product at least three times with no appreciable decrease in respective yield.

Basic 1-butyl-3-methylimidazolium hydroxide ([bmim]OH) ionic liquid was observed to catalyze the three-component condensation reaction of acid chlorides, amino acids, and dialkyl acetylenedicarboxylates in water. Functionalized pyrroles were obtained in high yields after reaction with this task-specific ionic liquid.[237]

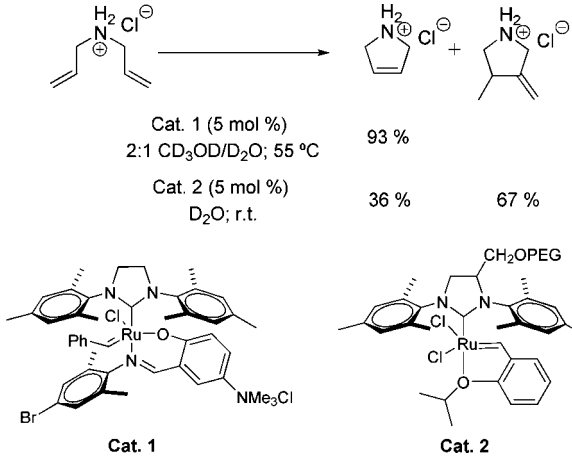
Recently, Chi et al.[238] described a novel ionic liquid methodology for pyrrole C-alkylation. Mono-C-alkylation of π-rich heteroatomic pyrrole by the Friedel−Crafts approach is impractical because the Lewis or Bronsted acid catalysts employed induce polymerization, ring opening, and polyalkylation.[239,240] Alternative methods for the preparation of C-alkyl pyrroles include the use of pyrrolylmagnesium halides[241,242] or isomerization of *N*-alkylpyrrole using thermal rearrangement at a very high temperature.[243] The traditional polar solvents such as DMSO, DMF, and THF are not appropriate for product isolation and media recycling processes. Several ionic liquids allowed pyrrole alkylation using various simple alkyl halides and mesylates selectively at C2 and C5 positions in moderate to good yields (55−82%) with minimal byproducts (<10%) under relatively mild conditions. The experimental procedure is very simple and convenient and does not involve any aqueous workup or Lewis acid/base catalyst.

2-(3-Phenylpropyl)pyrrole was synthesized from pyrrole and 1-bromo-3-phenylpropane using [bmim][SbF_6] in 71% yield in 44 h (using K_2CO_3) or 74% yield in 48 h (without the presence of K_2CO_3). For both cases, only 8−10% of

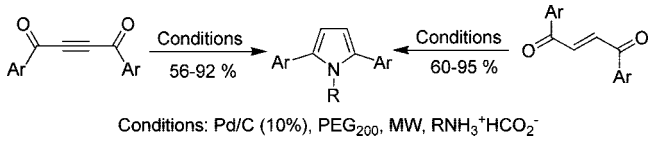
Scheme 36



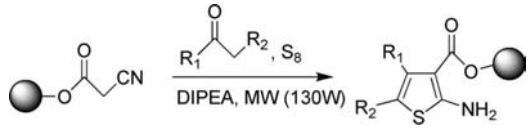
Scheme 37



Scheme 38

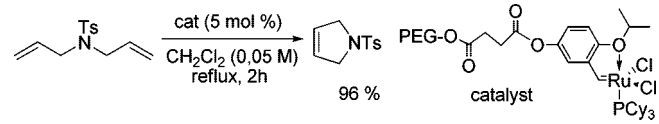


Scheme 39

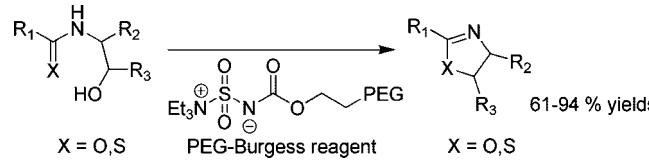


dialkylated compound was observed (Table 33). The same reaction in organic solvent such as acetonitrile hardly occurred even after 7 days (only 5% of desirable product). The addition of 10−30% of acetonitrile as a cosolvent allowed a complete solubilization of the salt formed during the reaction and did not affect the reactivity of the alkylation process. The [bmim][SbF_6]/acetonitrile system was described as better than other IL/organic solvent systems such as

Scheme 40



Scheme 41



[bmim][PF_6], [bmim][BF_4], [bmim][NTf_2], or [bmim][OTf] with toluene or 1,4-dioxane as cosolvents.

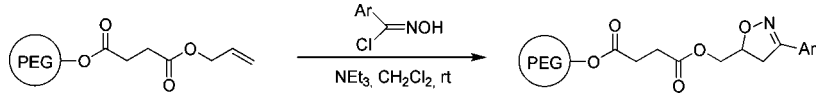
The authors also reported the efficiency of this methodology in the case of alkylation of pyrrole with primary, secondary, and benzylic halides or mesylates in moderate to high yields (55−82%) of corresponding pyrrole-α-alkylated products.[238]

More recently, these authors reported the same methodology for the N-alkylation of pyrrole using potassium or cesium carbonate in [bmim][BF_4] as the sustainable reaction media with acetonitrile as cosolvent.[244] The N-alkylated pyrroles were achieved in good yields using alkyl halides, as well as sulfonates, as electrophiles.

During the studies on pyrrole C-alkylation in ILs with 1-bromo-3-phenylpropane, the pyrrole carbamate was obtained as major product and the N-alkylated pyrrole as the minor byproducts, while the same reaction in the absence of pyrrole provided symmetrical dialkylcarbonate as the unique product. The formation of pyrrole carbamate (route A) and N-alkylated pyrrole (route B) could be explained assuming that the reactions follow two different routes as presented in Scheme 44.

The IL [bmim][BF_4] was used to prepare several amines by reductive amination from aldehyde kainic acid protected derivatives.[245] This protocol opens new possibilities toward the synthesis of potential conformationally constrained and

Scheme 42



Scheme 43

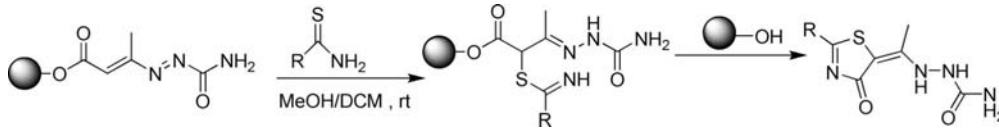
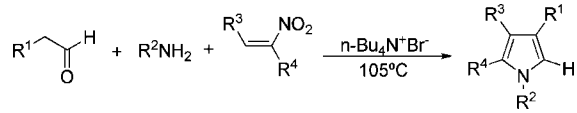
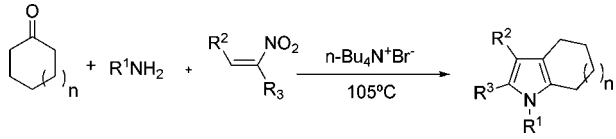


Table 29



Entry	R^1	R^2	R^3	R^4	Time (h)	Yield (%)
1	C_8H_{17}	$CH_3(CH_2)_3$	*p*-$(NO_2)C_6H_4$	CH_3	1	82
2	C_8H_{17}	C_6H_{12}	$C_8H_8O_2$	CH_3	1	75
3	C_8H_{17}	$PhCH_2$	$C_8H_8O_2$	CH_3	1	75
4	C_8H_{17}	C_6H_{12}	*p*-(Cl)C_6H_4	CH_3	1	80
5	C_8H_{17}	$PhCH_2$	*p*-(Cl)C_6H_4	CH_3	0.75	85
6	CH_3	$PhCH_2$	*p*-$(NO_2)C_6H_4$	CH_3	1	72
7	CH_3CH_2	$CH_3(CH_2)_2$	Ph	CH_3	1	70
8	CH_3		Ph	CH_3	1	73
9	CH_3CH_2	$CH_3(CH_2)_3$	Ph	CH_3	1	69
10	CH_3	$CH_3(CH_2)_3$	*p*-(Cl)C_6H_4	CH_3CH_2	1	70

Table 30

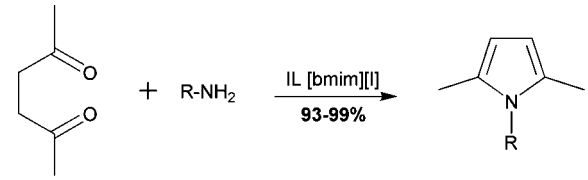


Entry	n	R^1	R^2	R^3	Time (h)	Yield (%)
1	1	C_6H_{12}	*p*-(Cl)C_6H_4	CH_3	1	87
2	1	Ph	*p*-(Cl)C_6H_4	CH_3	1.5	68
3	1	$PhCH_2$	*p*-(Cl)C_6H_4	CH_3CH_2	1	86
4	1		Ph	CH_3	0.75	83
5	1	$(CH_3)_2CH$	*p*-(Cl)C_6H_4	CH_3CH_2	1	73
6	1	$PhCH_2$	*p*-(Cl)C_6H_4	CH_3	0.5	92
7	2	$PhCH_2$	*p*-(Cl)C_6H_4	CH_3	1	80
8	3	$CH_3(CH_2)_3$	Ph	CH_3	1	71
9	3	$PhCH_2$	*p*-(Cl)C_6H_4	CH_3	0.75	85
10	3	$CH_3(CH_2)_3$	Ph	CH_3	1	69
11	3	$PhCH_2$	*p*-$(NO_2)C_6H_4$	CH_3	0.5	91
12	3	$PhCH_2$	$C_8H_8O_2$	CH_3	0.75	75

functionalized glutamic acid analogues or kainoid derivatives (Scheme 45).[246,247]

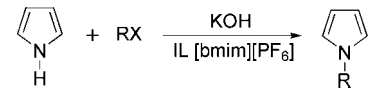
Cyclic *N*-acyliminium ions have been generated *in situ* at room temperature and functionalized by nucleophilic addition of allytrimethylsilane, silyl enol ethers, and ketene silyl acetals using IL [bmim][$InCl_4$] (Scheme 46).[248]

Table 31



entry	R	time (min)	yield (%)
1	*n*-propyl	30	96
2	*n*-heptyl	30	95
3	isopropyl	30	96
4	*t*-butyl	60	97
5	cyclohexyl	60	95
6	benzyl	30	99
7	phenyl	180	96 (94), reused 3 times
8	tolyl	180	94
9	*p*-nitrophenyl	180	93
10	*p*-methoxyphenyl	180	95
11	2-pyridinyl	180	85

Table 32



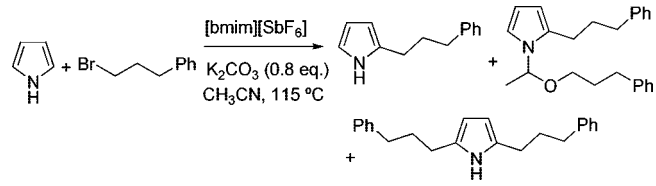
entry	RX	reaction conditions	yield (%)
1	CH_3I	2 h, 40 °C	82 (80[a])
2	*i*-C_3H_7Br	2 h, 60 °C	70 (65[a])
3	*n*-C_4H_9Br	1 h, 80 °C	cycle 1, 98 (95[a]) cycle 2, 96 cycle 3, 97
4	*n*-C_4H_9Cl	2 h, 80 °C	76 (73[a])
5	*t*-C_4H_9Br	2 h, 70 °C	57 (51[a])
6	CH_2=$CHCH_2Br$	1 h, 70 °C	100 (96[a])
7	$C_6H_5CH_2Br$	1 h, 80 °C	100 (98[a])
8	$C_6H_5CH_2Cl$	1 h, 80 °C	99 (98[a])
9	CH_2=CHCN	1 h, 80 °C	82 (80[a])
10	CH_2=$CHCO_2CH_3$	1 h, 80 °C	78 (72[a])
11	CH_2=$CHCOCH_3$	1 h, 80 °C	80 (75[a])
12	$C_6H_5SO_2Cl$	1 h, 80 °C	100 (99[a])
13	*p*-$CH_3C_6H_5SO_2Cl$	1 h, 80 °C	100 (98[a])
14	C_6H_5COCl	1 h, 80 °C	100 (98[a])

[a] Performed in [bmim][BF_4].

The *N*-acyliminium ions as electrophilic species[249] are usually generated from the corresponding α-haloalkyl, α-hydroxyalkyl, α-alkoxyalkyl, α-acyloxyalkyl, or α-sulfonyl precursors under the influence of a wide range of Lewis acids,[250,251] such as $TiCl_4$, $SnCl_4$, $InCl_3$, $NbCl_5$, or silylating agents (TMSOTf). Organoindate(III) ionic liquids were successfully employed without the need for an external Lewis acid allowing the preparation of the corresponding α-substituted heterocycles in good yields (75−80%). The ionic liquid phase could be reused at least three times.

Xia et al.[252] reported first the conjugate addition reaction of azide ion to α,β-unsaturated carbonyl compounds in

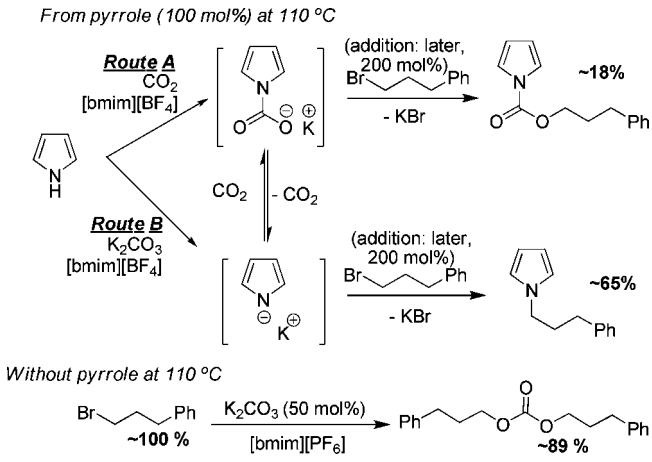
Table 33



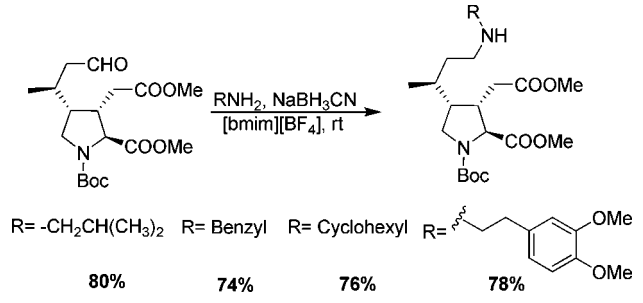
entry[a]	ionic liquid (mL)	organic solvent (mL)	time (h)	yield of product (%) recovered $Br(CH_2)_3Ph$	mono-alkylated	di-alkylated	N-alkylated
1	[bmim][SbF_6] (3)		44		71	10	
2[b]	[bmim][SbF_6] (3)		48		74	8	
3	[bmim][SbF_6] (2.7)	CH_3CN (0.3)	44		77	7	
4	[bmim][SbF_6] (2.4)	CH_3CN (0.6)	44		81	5	
5	[bmim][SbF_6] (2)	CH_3CN (1)	48		77	6	
6	[bmim][SbF_6] (1)	CH_3CN (2)	72	29	43	10	trace
7	[bmim][SbF_6] (0.5)	CH_3CN (2.5)	72	36	34	11	trace
8	[bmim][SbF_6] (0.1)	CH_3CN (2.9)	168	55	22	4	5
9[c]		CH_3CN (3)	168	85	5	4	trace
10[c]	[bmim][PF_6] (2.4)	CH_3CN (0.6)	46		68	2	21
11[c]	[bmim][NTf_2] (2.4)	CH_3CN (0.6)	48		65	3	24
12	[bmim][OTf] (2.4)	CH_3CN (0.6)	72	35	51	2	4
13[d]	[bmim][BF_4] (2.4)	CH_3CN (0.6)	45		25	2	2
14[e]	[bmim][SbF_6] (2.4)	Toluene (0.6)	46		57	10	2
15[e]	[bmim][SbF_6] (2.4)	1,4-dioxane (0.6)	46		60	8	2

[a] All reactions were carried out on a 1.0 mmol reaction scale of alkyl bromide with 10.0 equiv of pyrrole and 0.8 mmol of K_2CO_3 at 115 °C. [b] Reaction was carried out in the absence of K_2CO_3, and 4% yield of the hydroxylated compound, 1-hydroxy-3-phenylpropane, was detectable by ^{1}H NMR. [c] Trace of 1-(3-phenylpropyl)-1*H*-pyrrole was detectable by ^{1}H NMR. [d] 1-(3-Phenylpropyl)-1*H*-pyrrole (62% yield) and the eliminated compound, allybenzene (2% yield), were detectable by ^{1}H NMR. [e] Allybenzene (12% yield for entry 14, 10% yield for entry 15) and hydrolyzed compound, 3-hydroxypropylbenzene (2% yield), were detectable by ^{1}H NMR.

Scheme 44

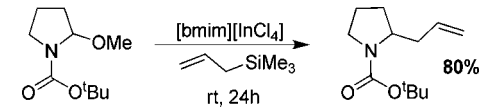


Scheme 45

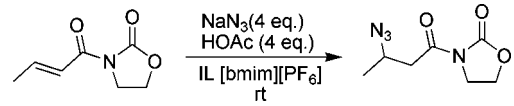


recyclable ionic liquids [bmim][PF_6] and [bmim][BF_4] as a new procedure for the aza-Michael reaction using NaN_3 directly. A crotonate derivative of 2-oxazolidinone was used to afford the azide derivate in 92% yield using sodium azide and HOAc in ionic liquids (Scheme 47). Several cyclic α,β-unsaturated ketones were proven to be excellent substrates

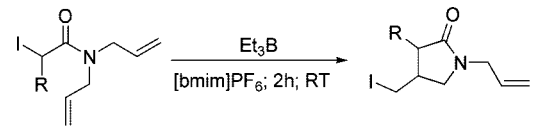
Scheme 46



Scheme 47



Scheme 48

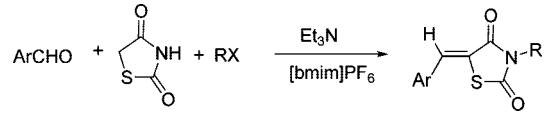


R=H
1 st run: 82%; 2 nd run: 85%
3 rd run: 86%; 4 th run: 81%
5 th run: 67%
R=CH_3: 87%

for this aza-Michael reaction such as *N*-phenyl maleimide (62%) and *N*-propyl maleimide (60%) in [bmim][BF_4] and [bmim][PF_6], respectively.

Radical cyclization reaction of *N*,*N*-diallyl-2-iodoacetamide was first reported in ionic liquids by Oshima and coworkers.[253] Triethylborane was added to amide (R = H) in IL [bmim][PF_6] as reaction medium and stirred under air at room temperature for 2 h. The corresponding lactam product (R = H) was extracted from the ionic liquid using ether giving 82% yield of pyrrolidin-2-one derivative, and the IL could be reused four times with a decreased yield only at the fifth cycle (67%). In the case of 2-iodopropanamide (R = CH_3), the cyclization proceeded similarly to afford the desired product in 87% yield (Scheme 48).

Table 34



entry	ArCHO	RX	solvent	temp (°C)	time (h)	yield (%)
1	PhCHO	MeI	[bmim][PF_6]	25	2	83 (1st) 83 (2nd)[a] 82 (3rd)[a] 84 (4th)[a]
2	PhCHO	MeI	[bmim][PF_6]	25	8	10[b]
3	PhCHO	MeI	DMF	25	10	40
4	PhCHO	MeI	MeCN	25	10	26
5	PhCHO	MeI	toluene	25	10	13
6	4-$MeOC_6H_4CHO$	MeI	[bmim][PF_6]	25	2	81
7	4-$NO_2C_6H_4CHO$	MeI	[bmim][PF_6]	25	2	62
8	PhCHO	$PhCH_2Cl$	[bmim][PF_6]	60	3	85
9	4-$MeOC_6H_4CHO$	$PhCH_2Cl$	[bmim][PF_6]	60	3	84
10	4- $NO_2C_6H_4CHO$	$PhCH_2Cl$	[bmim][PF_6]	60	3	70
11	PhCHO	4-$NO_2C_6H_4CHO$	[bmim][PF_6]	60	4	68
12	PhCHO	$Me(CH_2)_2CH_2Br$	[bmim][PF_6]	60	3	79
13	PhCHO	Me_2CHI	[bmim][PF_6]	60	3	75

[a] Results obtained using recycled IL [bmim][PF_6]. [b] Using K_2CO_3 as a base.

3-Alkyl-5-[(*Z*)-arylmethylidene-1,3-thiazolidine-2,4-diones display various biological and pharmaceutical activities, for example, as antitubercular, bactericidal, insecticidal, anthelmintic and fungicidal agents, and they are an important class of synthetic intermediates in organic synthesis.[254,255] A rapid one-pot synthesis of 3-alkyl-5-[(*Z*)-arylmethylidene-1,3-thiazolidine-2,4-diones has been described using ionic liquids as a novel solvent media (Table 34).[256] The authors observed that in the presence of Et_3N the reaction of benzaldehyde, 1,3-thiazolidine-2,4-dione, and methyl iodide in IL [bmim][PF_6] was completed within 2 h at room temperature resulting in the formation of 3-methyl-5[(*Z*)-phenylmethylidene]-1,3-thiazolidine-2,4-dione in 83% of yield (Table 34, entry 1). This reaction was also tested using K_2CO_3 instead of Et_3N, but the corresponding yield was only 10% even after a long reaction time of 8 h (entry 2). With conventional organic solvents such as DMF, MeCN, and toluene, the desired product was produced in lower yields (40%, 26%, and 13%, respectively) than with IL media (83%) (entries 3−5 vs entry 1).

The reaction of several aromatic aldehydes containing an electron-withdrawing substituent, such as a nitro group, or an electron-donating substituent, such as a methoxy group, different alkyl halides containing a chloro, bromo, or iodo group, and thiazolidine-2,4-dione in the presence of triethylamine in IL [bmim][PF_6] gave moderate to good yields (62−85%) of product, and an enhanced rate of reaction and selectivity were observed. The ionic liquid could be recovered by extracting the product and then washing the residue with water followed by vacuum drying. The IL [bmim][PF_6] was reused during four cycles with no appreciable decrease in yield (entry 1).

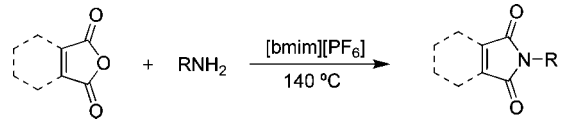
Cyclic imide derivatives are compounds of considerable interest due to their biological properties[257,258] and their use as intermediates in polymer chemistry[259] and in organic synthesis.[260,261] The general synthetic methods involve direct N-alkylation of phtalimide, succinimide, and maleimide with an alkylating agent combined with the use of an appropriate base such as BuLi,[262,263] Et_3N,[264] or NaH.[166] Other recent approaches for the preparation of imides include dehydrative condensation of an anhydride and amine at high temperature or cyclization of maleamic acid intermediates in the presence of acidic reagents.[265,266] All the methods described in the literature have presented some disadvantages, related to the long reaction time, high reaction temperature, and in some cases poor yields.[265−268]

Chen et al.[269] demonstrated that the synthesis of cyclic imide derivatives can be performed efficiently using the ionic liquids [bmim][PF_6], [bmim][BF_4], or [bmim][Cl] in excellent yields (Table 9). By this methodology, a series of succinimide, maleimide, and phtalimide derivatives were prepared from corresponding anhydrides with a variety of primary aliphatic, heterocycles, and aromatic amines containing different groups such as methyl, chloro, and nitro in high yields (90−98%, Table 9). Many advantages were observed using this new approach compared with those reported in the literature including the higher yields, operational simplicity, higher efficiency, and the possibility of ionic liquid recycling. Two comparative studies illustrate the advantage of this new approach: (a) the reaction of phtalic anhydride and aniline using *p*-cymene as solvent needed reflux overnight to give *N*-phenylphtalimide in 69% of yield,[270] while the same reaction in IL [bmim][PF_6] was completeted within only 5 min at 140 °C with 98% of yield; (b) the reaction of *N*-(1-naphthyl)succinimide by a traditional method using glacial acetic acid as solvent needed reflux for 30 min and storage at room temperature for 7 days yielding only 26% product,[271] while the synthesis in IL [bmim][PF_6] was performed in 20 min with 90% yield.

Simultaneously, the same authors[152] reported that the N-alkylation of phtalimide and several nitrogen heterocyclic compounds can be performed using ionic liquids [bmim][BF_4], [bmim][PF_6], or [buPy][BF_4] in the presence of potassium hydroxide as a base (Table 36).

Conventional methods involve direct N-alkylation of phtalimide, succinimide, and maleimide with an alkylating agent by treatment of these compounds with an appropriate base such as NaH, KH, or BuLi in organic solvent media such as DMF, THF, acetone, or DMSO.[272,273] With ionic liquids as alternative media, high yields, simplicity of methodology, and potential for recycling of ionic liquids were observed.

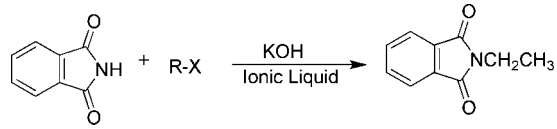
Table 35



entry	anhydride	amine	time (min)	yield (%)
1	succinic anhydride	phenylamine	20	96
2		*p*-clorophenylamine	20	95
3		*p*-methylphenylamine	20	96 (95)[a]
4		*p*-nitrophenylamine	5	97 (1st) 96 (2nd)[b] 97 (3rd)[b]
5		(1-napthyl)amine	20	90
6		(5-methyl-1,3,4-thiodiazol-2-yl)amine	5	99
7		benzylamine	20	92
8		butylamine	20	91
9	maleic anhydride	phenylamine	20	97 (88)[c]
10		*p*-clorophenylamine	20	95 (93)[a]
11		benzylamine	20	91
12		(1-napthyl)amine	20	93
13	phthalic anhydride	phenylamine	5	98 (98)[a]
14		benzylamine	5	96

[a] In IL [bmim][BF_4]. [b] Results obtained using recycled IL [bmim][PF_6]. [c] In IL [bmim][Cl].

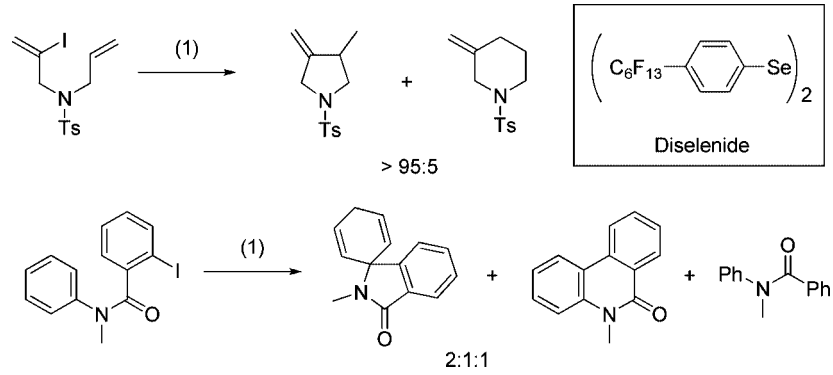
Table 36



entry	R−X	ionic liquid	reaction conditions	product	yield (%)
1	MeI	[bmim][BF_4]	40 °C, 5 h	*N*-methylphatlimide	91
2	EtBr	[bmim][BF_4]	40 °C, 5 h	*N*-ethylphatlimide	96 (1st) 94 (2nd)[a] 95 (3rd)[a]
3	EtBr	[bmim][PF_6]	40 °C, 5 h	*N*-ethylphatlimide	95
4	EtBr	[buPy][BF_4]	40 °C, 5 h	*N*-ethylphatlimide	97
5	PrBr	[bmim][BF_4]	60 °C, 5 h	*N*-propylphatlimide	93
6	i-PrBr	[bmim][BF_4]	50 °C, 5 h	*N*-isopropylphatlimide	78
7	BuBr	[bmim][BF_4]	80 °C, 5 h	*N*-butylphatlimide	94
8	BuBr	[bmim][PF_6]	80 °C, 5 h	*N*-butylphatlimide	92
9	BzBr	[bmim][BF_4]	80 °C, 2 h	*N*-benzylphatlimide	97
10	BzCl	[bmim][BF_4]	80 °C, 2 h	*N*-benzylphatlimide	96
11	BzCl	[buPy][BF_4]	80 °C, 2 h	*N*-benzylphatlimide	95
12	$ClCH_2CO_2Et$	[bmim][BF_4]	80 °C, 4 h	ethyl-*N*-phthalimidoacetate	92

[a] Results obtained using recycled IL [bmim][BF_4].

Scheme 49[a]



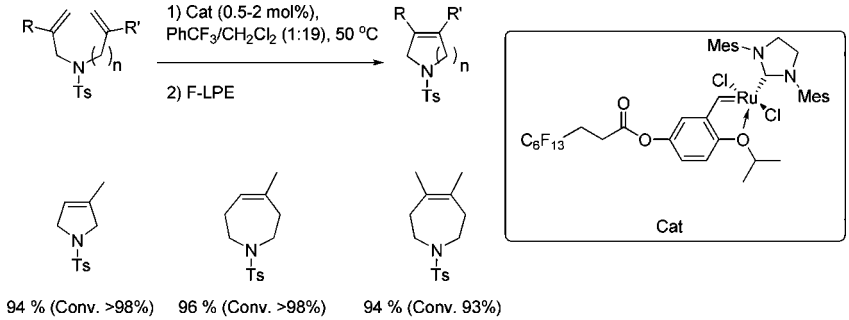
[a] (1) Bu_3SnH, AIBN, 80 °C; diselenide; continuous extraction (F-LPE).

4.1.5. Reactions in Fluorinated Fluids

Crich et al. developed a fluorous diaryl selenide to minimize the occurrence of some radical rearrangements.[274] This approach has been applied in the radical cyclization described in Scheme 49 allowing the recovery of fluorous areneselenol by continous extraction.[275]

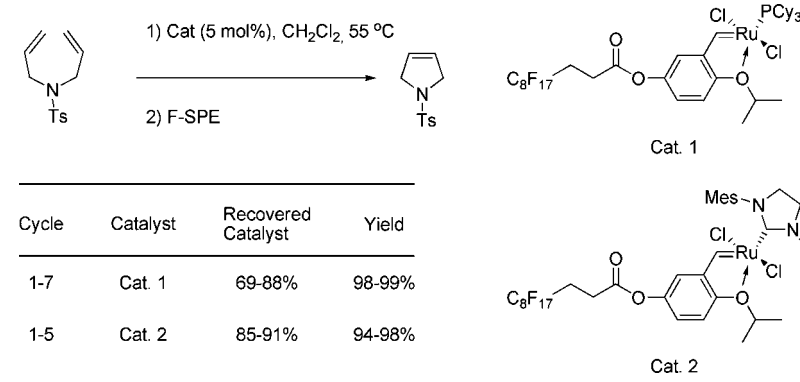
Ring-closing olefin metathesis (RCM) is a very powerful methodology for the synthesis of complex cyclic molecules.[276−278]

Scheme 50



Cycle	1-16	17-20	1-9	10-12	1-9	10-12
Conversion	>98%	97-94%	>98%	98-95%	>98%	98-95%

Scheme 51



Cycle	Catalyst	Recovered Catalyst	Yield
1-7	Cat. 1	69-88%	98-99%
1-5	Cat. 2	85-91%	94-98%

Yao et al. reported the efficient reuse of the RCM ruthenium catalyst by incorporation of a perfluoroalkyl group and the F-LPE process.[279] This approach has been applied to the synthesis of several nitrogen-based heterocycles (Scheme 50).

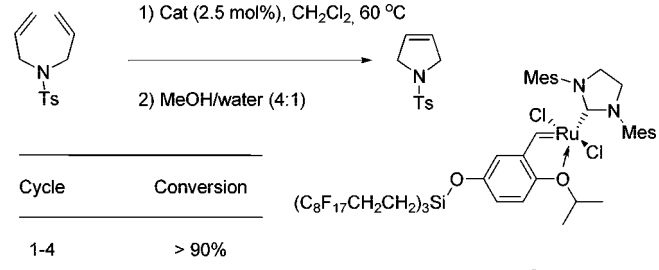
Later, Curran et al.[280] reported a similar approach based on the development of RCM ruthenium catalysts containing the C_8F_{17} fluorous tag. With *N*,*N*-diallyl-*p*-toluenesulfonamide as a model substrate, efficient formation of the corresponding 2,5-dihydro-1*H*-pyrrole product, isolation, and catalyst reuse by F-SPE were achieved by separation on fluorous silica gel just by selection of the appropriate solvent system, MeCN and Et_2O, respectively, for elution of the RCM product and RCM catalyst (Scheme 51).

Bannwarth et al.[281] reported a similar catalyst containing instead a tris(perfluoroalkyl)silyl tag that attached efficiently to fluorous silica gel. When the reaction is performed in dichloromethane, the catalyst is detached from the solid support. After the reaction, the solvent was evaporated and switched to MeOH/water (4:1), allowing the removal of the RCM product with minimal amount of catalyst (1% catalyst leaching) from the fluorous silica gel (Scheme 52). The reused catalyst (2.5 mol %) allowed high conversions for four runs.

Gladysz et al.[282] also reported analogues of Grubbs second generation catalyst containing fluorous phosphines $P[(CH_2)_mRf_n]_3$ ($m = 2, 3$; $n = 6, 8, 10$) and used them for RCM under F-LPE conditions.

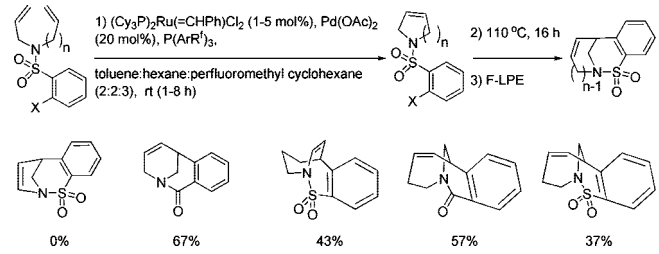
Grigg et al.[283] used the perfluorinated triarylphosphine to recycle the catalytic system and perform sequential RCM

Scheme 52



Cycle	Conversion
1-4	> 90%
5	~ 75%

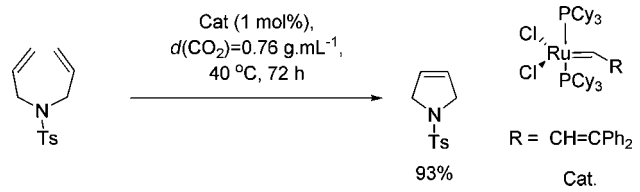
Scheme 53



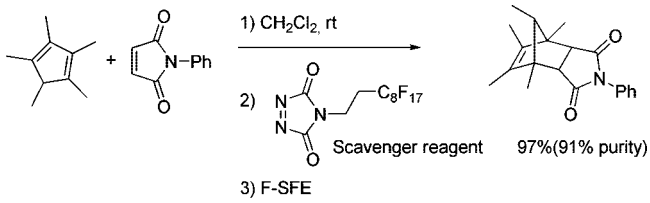
and intramolecular Heck reaction using a solvent system consisting of toluene/hexane/perfluoromethyl cyclohexane (2:2:3) at room temperature and 110 °C, respectively (Scheme 53).

Interestingly Curran et al. described the use of [1,2,4]-triazoline-3,5-dione containing fluorous tags as a scavenging

Scheme 54



Scheme 55

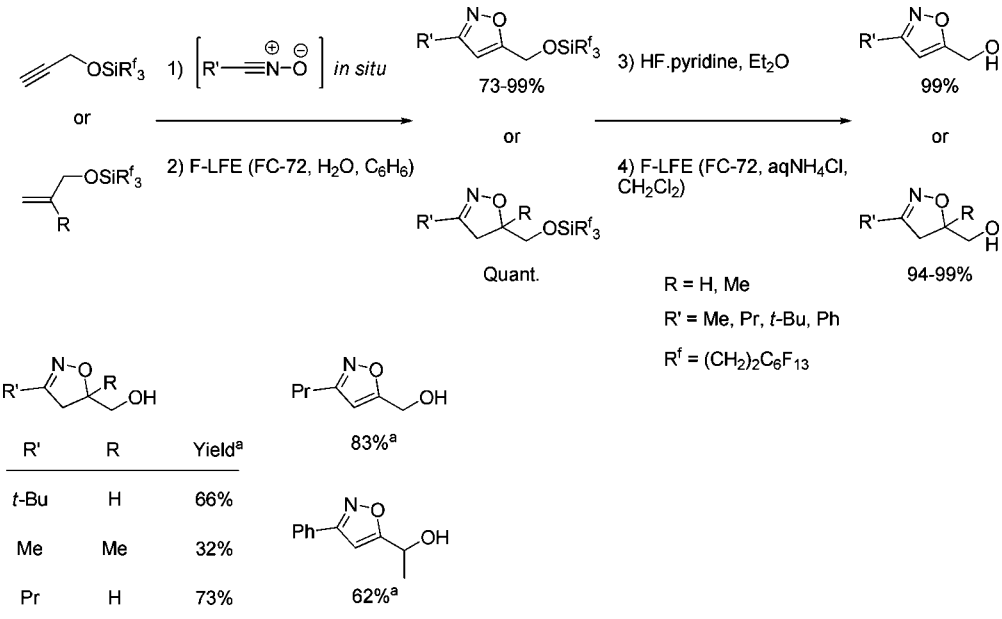


reagent of excess of diene after Diels−Alder (DA) reaction. The resulting fluorous DA adduct and the fluorous scavenger can be efficiently removed by F-SPE using FluoroFlash cartridges (Scheme 55).[286]

The fluorinated tags incorporated in reagents have been used by Curran et al. and other research groups to facilitate product isolation for different reactions.[63] Curran et al. described two elegant systems for product isolation in cycloaddition reactions, which allow easy isolation of the product containing the fluorous tag by their preferential partition to the fluorinated solvent, allowing the removal of non-fluorinated hydrophobic and hydrophilic product just by extraction with organic solvent and water. Final removal of the fluorous tag allows isolation of the desired non-fluorinated product in high purity without further purification. In Scheme 56, two examples are presented provided by the authors for the preparation of isoxazoles, isoxazolines, and tetrazoles.[287,288]

Hultin et al.[289] described a practical synthesis of fluorous oxazolidinone chiral auxiliaries in up to 20 g scale in five steps from chiral α-amino acids in an overall yield of up to 55%. The fluorous tag facilitates the purification process simply by F-SPE (Scheme 57).

Scheme 56



R'	R	Yield[a]
t-Bu	H	66%
Me	Me	32%
Pr	H	73%

[a] Obtained yields for overall reaction and isolation process 1-4 (final purity > 96%).

Takeuchi et al. reported the total synthesis of the cyclic tripeptide bistratamide H based on the use of a highly fluorous amino protecting group and multistep purification by F-LPE using FC-72 in which 15 steps of the total of 17 were purified by F-LPE (Scheme 58).[290]

4.1.6. Reactions in Supercritical CO_2

Leitner et al. demonstrated the possibility to perform RCM in $scCO_2$ for a considerable range of substrates in comparable yields to the ones otained in chlorinated solvents. In contrast, the catalyst acts in $scCO_2$ in a heterogeneous fashion. In Scheme 54 is presented one representative heterocyclic example.[284,285]

Sakanishi et al. reported the dimerization of benzothiophene in $scCO_2$ catalyzed by $Al_2(SO_4)_3$ supported on silica gel.[291] The CO_2 fixation reaction to produce useful organic molecules is extremely important from the environmental point of view.[292−294] In an interesting approach, Matsuda et al. reported the preparation of pyrrole-2-carboxylate by carboxylation of pyrrole using cells of *Bacillus magaterium* PYR 2910 (Scheme 59).[295]

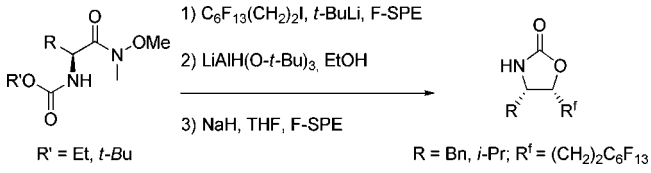
The chemical incorporation of CO_2 in $scCO_2$ was also described by Maggi et al. for the synthesis of oxazolidinones from propargylamines catalyzed by basic alumina (Scheme 60). The catalyst was recovered simply by filtration and efficiently reused for seven cycles.[296]

4.2. Containing Two Nitrogen Atoms

4.2.1. Solvent-Free Reactions

There are several procedures for the synthesis of imidazole ring systems, in which one depends on pretended substituents. For instance, imidazole-4-carboxylates can be obtained by an aza-annulation reaction of γ-dielectrophiles 4-dimethylamino-2-aza-1,3-dienes with hydrazines or amines. After several days at 70 °C (conventional heating), the desired imidazole derivatives can be obtained in moderate yields (Scheme 61).[297]

Scheme 57



Bridgehead heterocycles with an imidazole skeleton like imidazo[1,2-*a*]pyridines can be prepared through reaction of 2-aminopyridine and phenacyl bromide in the presence of neutral alumina at room temperature. Similarly, starting from 2-aminopyrimidine or 2-aminothiazoles, imidazo[1,2-*a*]pyrimidines or benzo[*d*]imidazo[2,1-*b*]thiazole can be achieved under the same reaction conditions.[298]

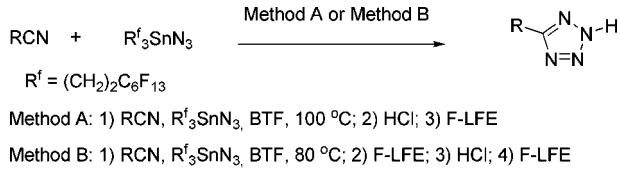
Solvent-free conditions have been explored through the use of silica gel or zeolite HY for the synthesis of tri- and tetrasubstituted imidazoles. Through microwave-induced condensation of benzil or benzaldehyde derivatives and ammonium acetate, trisubstituted imidazoles can be obtained in high yields in a few minutes (Scheme 62).[299] If an amine is added to the reaction mixture, tetrasubstituted imidazoles are obtained (Scheme 63).[300] Recently, it was observed that acidic alumina can also catalyze these reactions,[301] potassium dodecatungstocobaltate trihydrate ($K_5CoW_{12}O_{40}\cdot 3H_2O$) was reported as a reusable catalyst,[302] the use of ammonium acetate can be avoided by the utilization of benzonitrile derivatives,[303] the use of benzil can be replaced by benzoin with air functioning as an oxidant in the conversion,[304,305] or the reagents can be supported on silica gel/$NaHSO_4$ to perform the reaction under MWI or conventional heating conditions.[306] In the conventional heating procedure (140 °C), perchloric acid absorbed on silica gel was also reported to catalyze these reactions in good yields (56−98%).[307] Furthermore, it was observed that no inorganic support is needed, and the desired tri- or tetrasubstituted imidazoles can be obtained in excellent yields simply by microwave irradiation of the reaction components.[308] With recyclable silica sulfuric acid, 1,2-diketones, α-hydroxyketone, or α-keto-oximes can be condensed with an aromatic aldehyde and NH_4OAc through the conventional heating procedure at 130 °C or through MWI to give trisubstituted imidazoles in high yields (72−89%).[309]

The preparation of the synthetically valuable imidazole *N*-oxides can also be performed under solvent-free conditions by cyclization of 1,2-diimines with aldoximes after immobilization on an inorganic support (Table 38). It should be noted that the reaction yield is somewhat poor and it will depend on the acidity of the support used in conjugation with the diimine basicity; this way silica gel was reported as being more appropriate for the aromatic diimine cyclization, while more basic aliphatic diimines should be cyclized on neutral or weakly acidic alumina.[310]

For the modification of imidazole, 1,3-disubstituted imidazolium salts can be reacted with potassium thioacetate or potassium thiocyanate under microwave irradiation in order to synthesize 1,3-disubstituted imidazole-2-thiones. This way, imidazole-based ionic liquids can be easily transformed in other suitable reagents for organic synthesis when microwave irradiation is employed, but no reaction is observed under conventional heating.[311] The introduction of side chains in imidazole is a matter of great interest in the preparation of ionic liquids. In order to decrease the high excess of alkyl halide needed and to minimize the time-consuming preparation of 1-alkyl-3-methylimidazolium halides by conventional heating, it is now possible to synthesize them by microwave irradiation[201,312,313] or by sonochemical preparation.[314] For the *N*-propargylation of imidazole, Cs^+ saponites were developed as a good catalyst for this reaction, leading to the desired product in 100% selectivity and 90% yield.[315] Recently, an efficient system for the N-arylation of imidazole and benzimidazole derivatives was reported. The 2-aminopyrimidine-4,6-diol/CuBr/TBAF system was used in the coupling of such heterocyclic systems with aryl and heteroaryl halides in the absence of solvent at 145−150 °C for 24 h (Scheme 64). The use of CuCl and CuI was observed to be less efficient than use of CuBr, and from the several pyrimidines tested as ligands, the one with both hydroxyl and amino groups proved to be the best.[316]

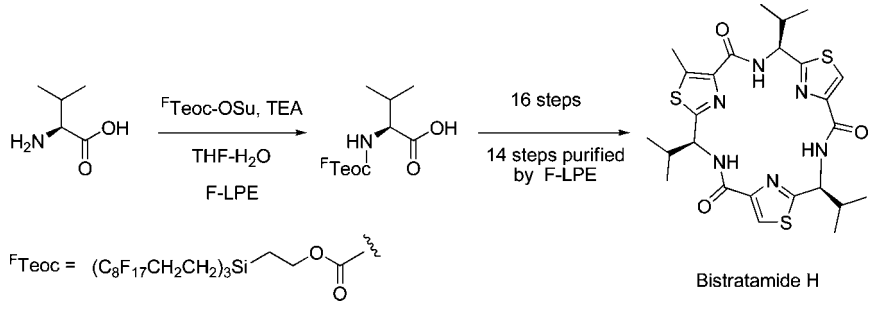
Imidazole was recently reported to react with epoxides at the less hindered carbon atom of the epoxide in solvent-free

Table 37

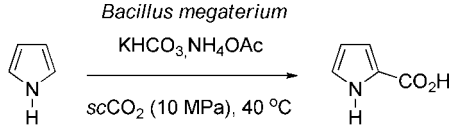


R	*p*-MeC_6H_4	*p*-$MeOC_6H_4$	$PhCH_2$	Ph	$PhMe_2C$	$Ph(CH_2)_4$	*t*-Bu	Me
method A (% yield)	99	95	98	99	96	21	55	
method B (% yield)	61	72	77	59			87	83

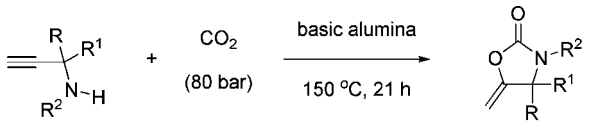
Scheme 58



Scheme 59



Scheme 60



conditions at 60 °C. Through this, alkyl substituents can be efficiently introduced in the nitrogen atom of the imidazole (72−92% yield).[317]

A versatile one-pot procedure for the synthesis of imidazo[1,2-*a*]pyridines through the use of MWI in dry media consists of irradiating a mixture of aldehydes and 2-aminopyridine in the presence of clay. After the generation of the iminium ion, an isocyanide is added and irradiated for some time more. This method proves to be extremely versatile since pyridine system can be replaced by other *N*-heterocycles like pyrazine or pyrimidine in order to obtain ring-fused imidazole systems (Scheme 65).[192,318]

Benzimidazoles can be prepared by MWI condensation of 1,2-phenylenediamine with carboxylic acids, acetoacetic ester,[319] or benzoic acid derivatives[193] in good yields in the absence of catalyst. In the case of aromatic carboxylic acids, hydrochloric acid was reported to be a good catalyst for the condensation with *o*-phenylenediamine.[320]

Montmorillonite KSF and K-10 are effective catalysts for the condensation of acetoacetate esters or orthoesters and aromatic orthodiamines in heterogeneous phase to afford arylimidazoles. As in the other cases, despite the reaction being performed under SFC, some solvent is needed to dissolve and immobilize the aromatic orthodiamine in the inorganic material. After solvent evaporation, the reaction mixture is irradiated with microwaves for 4 min.[321,322] Recently NaY zeolite was reported as a suitable catalyst for this transformation when aromatic carboxylic acids are used as the carbonyl species under microwave irradiation.[323] Similarly, 4-trifluoromethyl 1,2-phenylenediamine derivatives can react with aromatic aldehydes under microwaves in the presence of alumina and anhydrous zinc(II) chloride or $Na_2S_2O_5$ to result in the formation of the corresponding benzimidazoles in good yields (72−90%).[324−326] In the microwave-free version, $BF_3 \cdot OEt_2$[327] and $In(OTf)_3$[328] were reported to promote the condensation of *o*-phenylenediamines with aldehydes to yield benzimidazole derivatives while Bi(III) salts such as $Bi(TFA)_3$, $Bi(OTf)_3$, and $BiOClO_4$ were reported to be very good catalysts for the condensation of *o*-phenylenediamine with orthoesters at 80 °C. This last procedure was also studied for the formation of benzothiazoles, benzoxazoles, and oxazolo[4,5-*b*]pyridines starting from *o*-aminothiophenol, *o*-aminophenols, and 2-amino-3-hydroxy-pyridine, respectively.[329]

Two other methods for microwave-assisted preparation of benzimidazoles have been developed by condensation of 1,2-phenylenediamine with *in situ* generated chlorides of hydroxamic acids using alumina as support and reaction of the previous diamine and aryl aldehydes with silica-supported manganese dioxide (Scheme 66). This last method also proved to be successful for the preparation of benzoxazoline compounds by reaction of 2-aminothiophenol derivatives.[193] Recently, molecular iodine was reported to be a suitable catalyst for this transformation under microwave irradiation. However, starting from 2-aminothiophenol, 2-substituted benzothiazoles could be prepared at room temperature in short reaction times and good yields (10−20 min, 73−93% yield).[330] For this last transformation, zirconium(IV) oxide chloride ($ZrOCl_2 \cdot 8H_2O$) and copper(II) sulfate were also reported as good catalysts for the microwave-induced reaction, and the anhydrides could be used instead of the aldehydes.[331]

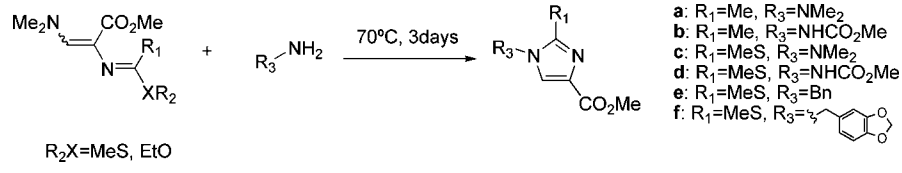
The Michael addition of cyanamide to 1,2-diaza-1,3-butadiene and subsequent intramolecular ring closure is a useful method for the preparation of 1,2-diaminoimidazoles in moderate yields under SFC and conventional heating at 50 °C.[332]

The highly valuable 2-trifluoromethylarylimidazoles can be prepared in good yields by cyclization of *ortho*-arylenediamines in the presence of montmorillonite K-10 under microwave irradiation (Scheme 67).[333] As a way to prepare hemicyanine dyes, quaternary salts of benzimidazoles can be condensed under MWI with aromatic aldehydes in presence of piperidine.[334]

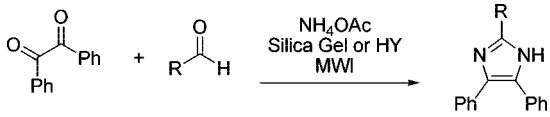
In order to introduce new substituents in a 2-alkylated benzimidazole derivative, this can be reacted with an isocyanate or isothiocyanate under solvent-free conditions at 48 °C (conventional heating) to yield tricyclic benzimidazole derivatives in good yields (up to 82%) (Scheme 68).[335] Modified benzothiazole analogues can be reacted with 1-(chloroalkyl)-4-substituted piperazines under MWI using alumina as inorganic support in the presence of sodium hydroxide to afford examples of serotonin $5HT_3$ receptor antagonists in reasonable yields.[336]

The synthesis of 4-alkylidene-1*H*-imidazol-5(4*H*)-one derivatives can be achieved by MWI 1,3-dipolar cycloaddition of an imidate and aromatic aldehyde (or an aldimine) in the presence of acetic acid as catalyst (Scheme 69).[337] In the absence of catalyst, imidazolone derivatives can also be achieved under similar conditions by using an amino alcohol and the same imidate[338] or can be condensed with aromatic aldehydes in the presence of $ZnCl_2$ under conventional heating (80−110 °C) to yield the π-conjugated heterocyclic system as the *Z* diastereoisomer.[339] On the other hand, 2-imidazolin-5-ones can be prepared from the condensation of an imidate and isocyanates or isothiocyanates at 70 °C[176]

Scheme 61



Scheme 62



R= Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-NOC_6H_4, 4-ClC_6H_4, 2-HOC_6H_4, 2,6-ClC_6H_3, 4-$Me_2NC_6H_4$

and pyrazolino/iminopyrimidino/thioxopyrimidino imidazoline derivatives can be obtained on basic alumina under MWI.[340]

Several derivatives of (5*Z*)-5-arylidene-3,5-dihydroimidazol-4-ones have been prepared through Knoevenagel reaction of aromatic aldehydes or cyclic ketones and 3-methyl-2-methylsulfanyl-3,5-dihydroimidazol-4-one in presence of piperidine as catalyst under microwave irradiation (Scheme 70). The reaction times decreased compared with the conventional heating in dichloromethane due to the high concentration of the reactants under SFC.[341] Some *N*-alkyl derivatives of leucettamine B were prepared under SFC by reaction of 2-thiohydantoin or 2-methylsulfanyl-3,4-dihydroimidazol-4-ones and an imine. The guanylation of 2-thiohydantoin with an amine (in large excess, 7−10 equiv), despite the long reaction times (2−7 days at 50 °C), leads to the formation of the desired leucettamine B in moderate yields (Scheme 71).[342] Furthermore, alkylaminomethylidene derivative synthesis of 2-thiohydantoins was performed by transamination also under solventless conditions in yields up to 88%.[343]

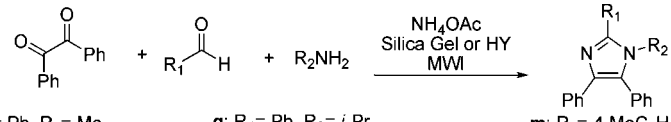
Through the use of microwave irradiation, imidazoline-2-one derivatives can be obtained, although in low yields (35−46%), using a $ZnCl_2/AlCl_3$ 1:3 mixture in silica as catalyst in the reaction of phenylglyoxal, alkylacetoacetates (or acetylacetone), and dimethylurea. Curiously, the use of urea instead of dimethylurea led to the formation of 3,4-dihydropyrimidinones under the same reaction conditions (26−42%).[344]

The synthesis of 2,4,5-triarylimidazolines in SFC can be performed by reaction of methanediamines (formed by reaction of aromatic aldehydes and hexamethyldisilazane (HMDS) under alumina-supported MWI) with base addition (DBU or DBN). The base choice and the irradiation time dictates the diastereoselectivity of the final product.[345] The *in situ* formation of a diamine or one step formation of the final imidazoline can also be achieved by conventional heating at 120 °C of the aromatic aldehyde and HMDS (Scheme 72).[346]

Long-chain 2-alkyl-1-(2-hydroxyethyl)-2-imidazolines can be synthesized in higher yields under MWI than by conventional heating synthesis through the condensation of aminoethylethanolamine and fatty acids, using CaO as reaction support.[347] A recent procedure for the preparation of *N*-tosyl-imidazolines, through the use of scadium triflate Lewis acid, can be adopted in order to avoid the use of microwaves. The cycloaddition of *N*-tosyl-2-arylaziridine and a nitrile in the presence of 25 mol % $Sc(OTf)_3$ at room temperature leads to the formation of the corresponding imidazoline, after a few minutes, in good yields (Scheme 73).[348] Based on this procedure, several metal triflates were studied as possible catalysts for this reaction, and zinc triflate was observed to be the best among several others.[349] Recently, elemental sulfur was reported as a suitable support for the solvent-free reaction between a nitrile and ethylenediamine under MWI to afford 2-imidazolines in reasonable to good yields (42−98%),[350] and reusable $ZrOCl_2 \cdot 8H_2O$ was observed to be a suitable catalyst for this reaction under microwave or ultrasonic conditions.[351] For the preparation of iminoimidazolines, the use of microwave irradiation was observed to induce the reaction of imidazoline-2-thione with aromatic amines in silica in reasonable yields (57−78%).[352]

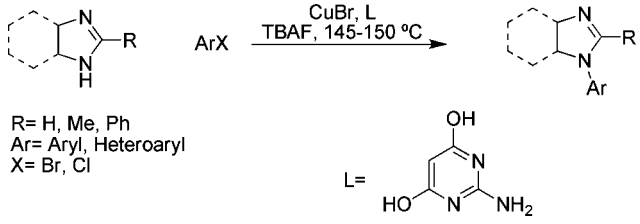
The conventional synthesis of 1,2,4-oxadiazoles proceeds through the O-acylation of an amidoxime with an acid chloride or with a carboxylic acid in the presence of a coupling reagent. This procedure was also performed under solvent-free conditions. Unfortunately, the carboxylic acid coupling in alumina does not result in respectable yields when microwave irradiation is used.[353] However, with the acid chloride in the presence of alumina-supported ammonium fluoride, good yields of the expected oxadiazole are obtained in 3 min under MWI (Scheme 74).[354] Recently, aldehydes were reported as suitable substitutes of acid chlorides when a catalytic amount of acetic acid is used under microwave conditions.[355] Also in the microwave preparation of 1,2,4-oxadiazoles, acid chlorides were substituted by Meldrum's acids and excellent yields of (81−98%) were obtained after 1 min of MWI.[356] Similarly, malonic diesters can react with amidoximes under conventional heating conditions (120−150 °C) to yield such heterocycles in 2−6 h.[357] Recently, methyl levulinate was reported to react with amidoxime under microwave conditions in the presence of potassium carbonate to yield 1,2,4-oxadiazoles after 5−10 min of irradiation,[358] and β-keto esters were observed to react with amidoxime under conventional heating conditions (120 °C, 2 h).[359] To circumvent the use of amidoxime, a new one-pot method based on the reaction of nitriles with hydroxylamine hydrochloride in the presence of magnesia-supported sodium carbonate followed by reaction with acyl halides was developed. Corresponding 1,2,4-oxadiazoles can be obtained in reasonable yields (40−70%) after brief irradiation with microwaves.[360] Another procedure for the synthesis of this type of compound has been developed through microwave-induced 1,3-dipolar cycloaddition of nitriles with a nitrile oxide. Despite the reasonable yields obtained with this procedure, the use of nitrones to achieve 2,3-dihydro-1,2,4-oxadiazoles resulted in low yields, which can be explained by the low stability of the products formed.[361]

Scheme 63

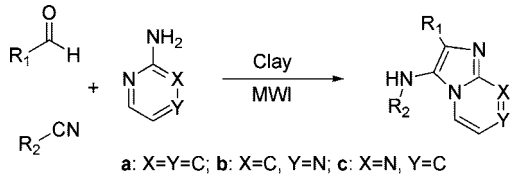


a: R_1= Ph, R_2= Me
b: R_1= 4-$CH_3C_6H_4$, R_2= Me
c: R_1= 4-BrC_6H_4, R_2= Me
d: R_1= Ph, R_2= Et
e: R_1= 4-MeC_6H_4, R_2= Et
f: R_1= 4-BrC_6H_4, R_2= Et
g: R_1= Ph, R_2= *i*-Pr
h: R_1= Ph, R_2= CH_2=$CHCH_2$
i: R_1= 4-BrC_6H_4, R_2= CH_2=$CHCH_2$
j: R_1=Ph, R_2= *i*-Bu
k: R_1= 4-MeC_6H_4, R_2= *i*-Bu
l: R_1= Ph, R_2= C_8H_{11}
m: R_1= 4-MeC_6H_4, R_2= C_6H_{11}
n: R_1= Ph, R_2= Ph
o: R_1= 4-MeC_6H_4, R_2= Ph
p: R_1= Ph, R_2= Bn
q: R_1= 4-MeC_6H_4, R_2= Bn

Scheme 64

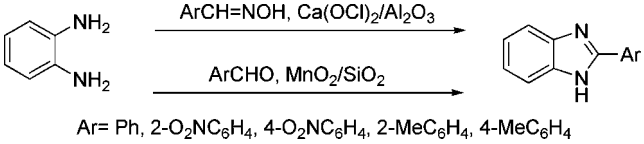


Scheme 65

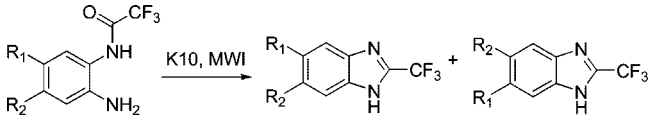


a: X=Y=C; **b**: X=C, Y=N; **c**: X=N, Y=C

Scheme 66



Scheme 67



a: R_1= R_2= H, **b**: R_1= R_2= Me, **c**: R_1= NO_2, R_2= H, **d**: R_1= Cl, R_2= H, **e**: R_1= H, R_2= Me, **f**: R_1= CO_2Et, R_2= H, **g**: R_1= H, R_2= CO_2Et

The preparation of 2,5-disubstituted 1,3,4-oxadiazoles can be achieved in good yields (78−89%) by oxidation of 1-aroyl-2-arylidene hydrazines with potassium permanganate on the surface of silica gel under microwave irradiation.[362] Recently, 1,3,4-oxadiazole derivatives containing the 4-nitroimidazole moiety were prepared under microwave irradiation of 2-methyl-4-nitro-imidazo acethydrazide with a carboxylic acid in the presence of phosphorous oxychloride (54−75% yield).[363] Through the use of acids as catalyst, the simple mixing of neat orthoesters with an acyl hydrazide was reported to be an efficient procedure for the preparation of 2,5-disubstituted 1,3,4-oxadiazoles (Table 39). Of all the acids studied as possible catalysts for this reaction, silica sulfuric acid was observed to be the most effective with the advantage that this could be easily recycled through washing products with ethanol.[364]

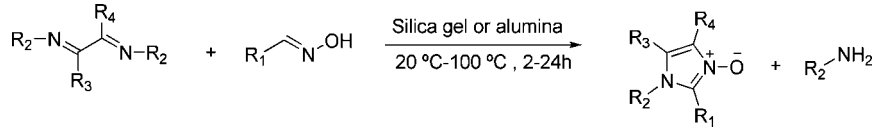
Pyrazole derivatives can also be efficiently prepared by simple grinding of a diketone and a hydrazine (Scheme 75, entries a−i) or hydrazide (Scheme 75, entries j,k) in a mortar with a small amount of sulfuric acid. Better results were attained with this procedure than in conventional solvent, but when asymmetric diketones are used, two regioisomers can be produced (Scheme 75).[365] The previous zirconium sulfophenyl phosphate (α-$Zr(CH_3PO_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$) is also an efficient catalyst for the preparation of pyrazoles through condensation of hydrazine and diketones at 40 °C (conventional heating). Furthermore, this procedure can also be used for the preparation of indazoles starting from 2-acetylcyclohexanone.[366] The Diels−Alder reaction between 4- or 5-vinylpyrazoles and a dienophile to produce indazole derivatives under MWI and SFC proved to be inefficient, resulting in the indazole derivatives in poor yields; however bipyrazoles can be produced in good yields and short reaction times through cycloaddition of pyrazolyl hydrazones and electron-poor dienophiles.[367,368] About the chiral preparation of 4-substituted pyrazoles, it can be achieved in a few minutes by reacting enantiopure 2-formyl glycals and aryl hydrazines under MWI.[369] Recently, methanesulfonic acid was reported to be an efficient catalyst for the solvent-free reaction of a β-keto nitrile with a hydrazine at 80 °C for 5−8 min to yield 3-amino-2*H*-pyrazoles in 90−98%.[370]

Recently, 1,2,3-triazoles were tested as dienes in Diels−Alder reaction with dimethyl acetylenedicarboxylate. In this microwave-induced reaction, silica-bound $AlCl_3$ was used as Lewis acid catalyst (0.1 mol %) for the formation of pyrazole-3,4-dicarboxylates after the extrusion of the substituent on position 4 of the triazole as a nitrile (Table 40). This method was reported as the first example of a reaction in which 1,2,3-triazoles were used as efficient dienes toward Diels−Alder reaction; furthermore, the use of silica-bound $AlCl_3$ allowed the reutilization of this catalytic system up to five times without any decrease in the product yield.[371]

The reaction of 1,1,1-trichloro-4-alkoxy-3-alken-2-ones with methyl hydrazine carboxylate under microwave irradiation in the absence of any inorganic support was observed to be an efficious method for the preparation of 5-trichloromethyl-4,5-dihydro-1*H*-1-pyrazole methyl esters (Scheme 76).[372]

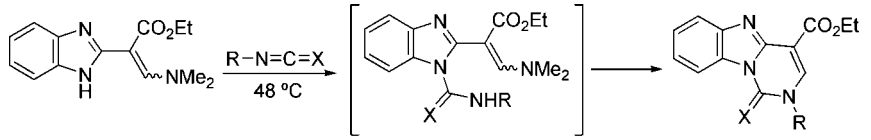
1,3,5-Trisubstituted 2-pyrazoles can also be efficiently obtained by oxidation of the corresponding pyrazolines by reaction with silica-supported *N*-bromosuccinimide[373] or 1,3-dibromo-5,5-dimethylhydantoin[374] under microwave irradiation. Fused pyrazole derivatives can be obtained in a couple of minutes by condensation of β-chlorovinylaldehydes with a hydrazine under microwave irradiation in the presence of a catalytic amount of *p*-TsOH (Scheme 77).[375] This last procedure was recently adapted to the synthesis of 1-(*p*-tosyl)pyrazolo[3,4-*b*]- (R_1 = $SO_2C_7H_7$) and 1-(2′,4′-dinitrophenyl)-pyrazolo[3,4-*b*]quinolines (R_1 = $C_6H_3(NO_2)_2$) in good to excellent yields (74−97%).[376]

Table 38

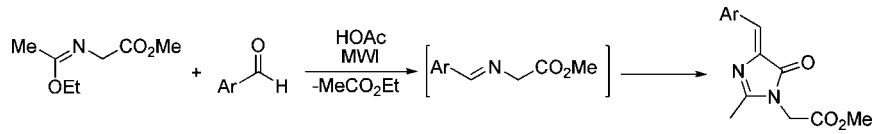


entry	R_1	R_2	R_3	R_4	support	temp (°C)	time (h)	yield (%)
1	$PhCH_2$	4-MeC_6H_4	Me	Me	silica gel	20	24	47
2	Ph	4-MeC_6H_4	Me	Me	silica gel	100	2	18
3	$PhCH_2$	cyclohexyl	H	H	alumina (pH = 3.8)	20	24	12
4	H	cyclohexyl	H	H	alumina (pH = 7)	20	14	42
5	Me	4-MeC_6H_4	H	H	alumina (pH = 7)	20	14	36

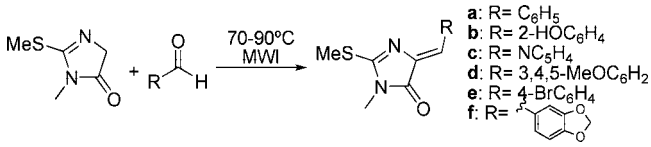
Scheme 68



Scheme 69



Scheme 70



Hydropyrazolopyridine can be obtained through reaction of pyrazole derivative with an alkene in the presence of catalytic *p*-TsOH under conventional heating.[377] For the introduction of N-substituents in pyrazole, there are several methods available; for instance, the preparation of pyrazole substituted with a carboximidamide moiety can be rapidly achieved through the reaction of pyrazole with a cyanamide and an organic or inorganic acid.[378] On the other hand, the N-alkylation of pyrazole can be achieved by reaction with 2,2′,4′-trichloroacetophenone under microwave irradiation. This last procedure proved to be efficient for other N-heterocycles like indazole and imidazole.[379] N-Alkylation of pyrazole, as with other heterocycles, can be successfully achieved at room temperature through reaction of the desired heterocycle with an epoxide in the presence of ytterbium triflate as catalyst,[380] while N-arylation can be performed through the use of copper catalysts with phosphine oxide ligands.[381]

The formation of two heterocyclic rings in one synthetic step has been developed for the preparation of coumarin derivatives. In this procedure, the thiazole ring is achieved by Hantzsch reaction followed by formation of pyrazole by reacting a 3-(2-bromoacetyl) coumarin with thiosemicarbazide and acetylacetone at room temperature (Scheme 78).[382]

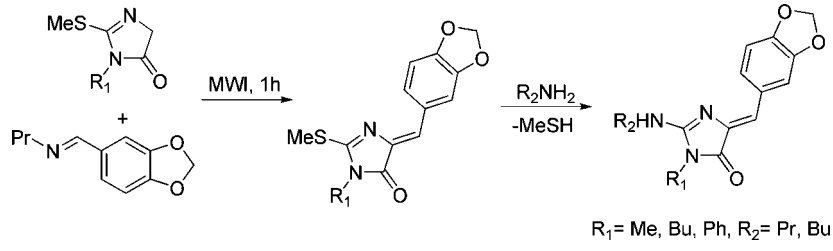
Through the use of reusable Zn[L-proline]$_2$ as catalyst, the hydrazones of 3-acetyl-4-hydroxycoumarin undergo ring cyclization to give 3-methyl-1-substituted phenyl-1*H*-chromeno[4,3*c*]pyrazol-4-ones (82−93% yield) under microwave irradiation and using neutral alumina as the inorganic support.[383]

Pyrazolines can be obtained in good yields by 1,3-dipolar cycloaddition between diphenylnitrilimine and an olefin on the surface of porous calcium hydroxyapatite (*p*-HAP300),[384] alumina,[385] or montmorillonite K-10[386] irradiated with microwaves (Scheme 79). Diphenylnitrilimine is generated *in situ* by reaction of hydrazonoyl chloride with the support acting as base in some cases. Despite the fact that the inorganic support should be chosen according to the olefin used, this procedure was successfully employed in the preparation of *spiro*-rhodanine-pyrazolines in presence of alumina.[385] Pyrazolines can also be produced through reaction of chalcones and silica gel-supported phenylhydrazine under microwave irradiation[387] or by microwave-induced condensation of a Michael acceptor with phenylhydrazine using $KHSO_4 \cdot H_2O$ impregnated on silica.[388]

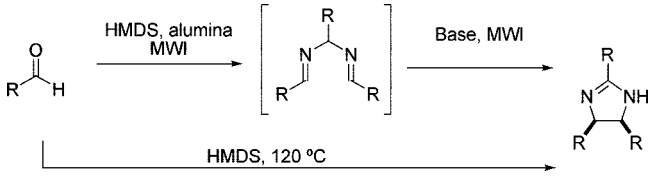
A procedure for the synthesis of 1-thiocarbamoyl-3,5-diphenyl-2-pyrazoline derivatives by reaction of chalcones and thiosemicarbazide through MWI has been developed (Scheme 80). The use of K_2CO_3 or basic alumina has proven very useful as reaction media support. Despite similar yields being obtainable on both supports, the reaction in basic alumina is faster, but the use of K_2CO_3 simplifies the work-up procedure in a way that only addition of water is needed.[389]

For the synthesis of pyrazolone derivatives, β-keto esters can be made to react with a hydrazine under microwave irradiation up to 3 min resulting in the desired product in good to excellent yields (86−94%). However when 2 equiv of the β-keto ester are used, 1*H*,6*H*-pyrano[2,3*c*]pyrazol-6-one derivatives are obtained in excellent yields (86−95%).[390,391] By reaction of hydrazines with 3-dimethylamino acrylates under solvent-free conditions (under conventional heating or microwave irradiation), 1,2-dihydropyrazol-3-ones can be obtained in good yields through an aza-annulation reaction (Scheme 81).[392] Chromones can also be attached to a pyrazolinone through condensation of this heterocycle with chromone aldehyde derivatives under MWI in the presence or absence of alumina as inorganic support.[393] Through the solid-state reaction of an aldehyde, indole, and 1-phenyl-3-methyl-5-pyrazolones in the presence of a catalytic amount

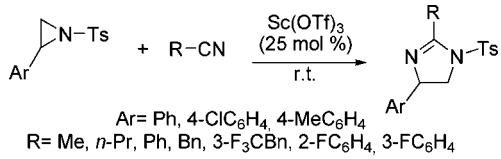
Scheme 71



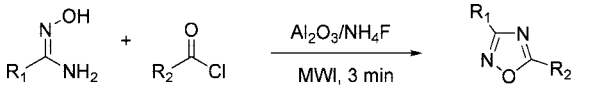
Scheme 72



Scheme 73

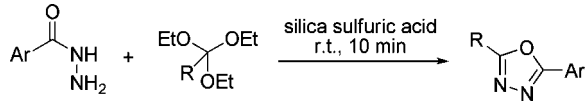


Scheme 74



a: R_1= R_2= Ph
b: R_1= 4-ClBn, R_2= Ph
c: R_1= 4-ClC_6H_4, R_2= Ph
d: R_1= 2,4-ClC_6H_3, R_2= Ph
e: R_1=C_6H_{11}, R_2= Ph
f: R_1= Ph, R_2=4-$MeOC_6H_4$
g: R_1= 2,4-$Cl_2C_6H_3$, R_2= 4-$MeOC_6H_4$
h: R_1= 4-ClBn, R_2= 4-$O_2NC_6H_4$
i: R_1= 4-ClC_6H_4, R_2= 4-$O_2NC_6H_4$
j: R_1= C_6H_{11}, R_2= 4-$O_2NC_6H_4$

Table 39

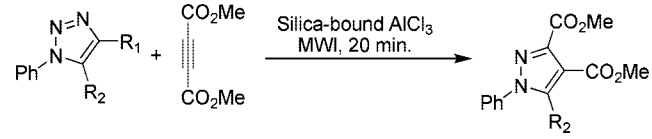


entry	Ar	R	yield (%)
1	4-ClC_6H_4	H	92
2	4-ClC_6H_4	Me	90
3	4-ClC_6H_4	Et	94
4	4-ClC_6H_4	Pr	90
5	4-ClC_6H_4	Pr	87
6	4-ClC_6H_4	Ph	90
7	3-$NO_2C_6H_4$	H	88
8	3-$NO_2C_6H_4$	Me	85
9	3-$NO_2C_6H_4$	Pr	93
10	3-$NO_2C_6H_4$	Bu	80
11	3-$NO_2C_6H_4$	Ph	85
12	Ph	Me	93
13	Ph	Ph	90
14	Ph	H	91
15	Ph	Et	93
16	Ph	Pr	89
17	Ph	Bu	95
18	4-pyridyl	Ph	87

of molecular iodine (10 mol %), 4-[(indol-3-yl)-arylmethyl]-1-phenyl-3-methyl-5-pyrazolones can be obtained in good yields (72−93%) after 2 h at room temperature, making this a suitable reaction for the introduction of a new substituent in the 4-position of the pyrazolone moiety.[394]

Recently, the cyclocondensation of aromatic aldehydes, malonitrile, and 3-methyl-1-phenyl-2-pyrazolin-5-one in the presence of 20 mol % of proline was reported. The procedure consisted of grinding the mixture for 5 min, yielding the

Table 40



entry	R_1	R_2	yield (%)
1	H	H	40
2	Ph	H	58
3	CHO	H	35
4	CO_2Me	H	38
5	Ph	CH_3	57
6	CH_3CH_2	CH_3CH_2	89
7	CH_3OCH_2	CH_3OCH_2	94
8	$CH_3(CH_2)_3$	$CH_3(CH_2)_3$	86

corresponding pyrans and pyrano[2,3-*c*]pyrazole derivatives in excellent yields (Table 41). It was observed that aldehydes containing electron-withdrawing substituents lead to better yields, while the position on the ring had no notable influence.[395]

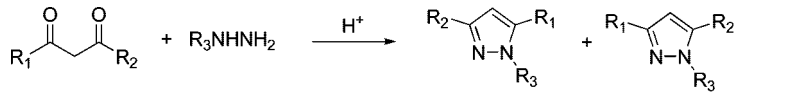
2-Amino-5-aryloxymethyl-1,3,4-thiadiazoles can be efficiently synthesized through reaction of thiosemicarbazide and carboxylic acids, using PEG-supported dichlorophosphate under MWI for 8−10 min (Scheme 82)[396] or employing acidic alumina as support.[397] Coumarin− and benzofuran−carboxamide substituents can be introduced in the thiadiazole ring by MWI or at room temperature in good yields and short reaction times.[396]

4.2.2. Reactions in Aqueous Media

Pyrazoles are known for their impressive biological activity as potent inseticides, herbicides and antitumor, anti-inflamatory, antimicrobial, and antipsychotic agents. The synthesis of these important molecules was reported in water through a novel 1,3-dipolar cycloaddition of diazocarbonyl compounds to alkynes catalyzed by $InCl_3$. The reaction of ethyl diazoacetate with ethyl propionate in the presence of 20 mol % $InCl_3$ afforded 87% of a pyrazole derivative. According to the authors, this product derived from a 1,3-dipolar cycloaddition and a spontaneous 1,3-hydrogen migration, Scheme 83.[398] Interestingly, the aqueous phase containing the catalytic system after work-up retained the ability to catalyze this transformation. This system was reused in two consecutive cycles affording the desired product in 89% and 90% yields, respectively.[398]

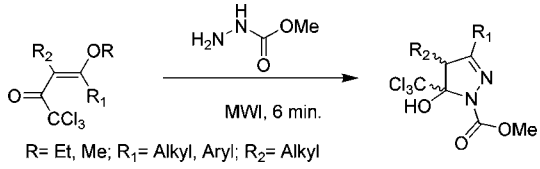
To explore the reaction nature, several diazo compounds with different electronic patterns were evaluated. As summarized in Table 42, all diazo substrates gave two pyrazoles in excellent combined yields, though the pyrazole that results from the aryl migration predominates in all cases. The aryl substituents exerted a small electronic effect over the reaction course. The aryl group with electron-donating substituents has a higher migratory tendency, and this trend suggests that this group is migrating to an electron-deficient carbon. Regarding these observations, the authors suggested a

Scheme 75



a: R_1= R_2= Me, R_3= Ph
b: R_1= R_2= Me, R_3= 4-MeC_6H_4
c: R_1= R_2= Me, R_3= H
d: R_1= R_2= *t*-Bu, R_3= H
e: R_1= R_2= *t*-Bu, R_3= Ph
f: R_1= CO_2Et, R_2= Me, R_3= H
g: R_1= Me, R_2= CO_2Et, R_3=Ph
h: R_1=Me, R_2= R_3= Ph
i: R_1= Me, R_2= Ph, R_3= H
j: R_1= R_2= Me, R_3= MeCO
k: R_1= R_2= Me, R_3= PhCO

Scheme 76



tentative mechanism, illustrated in Scheme 84, for the formation of both products.[398]

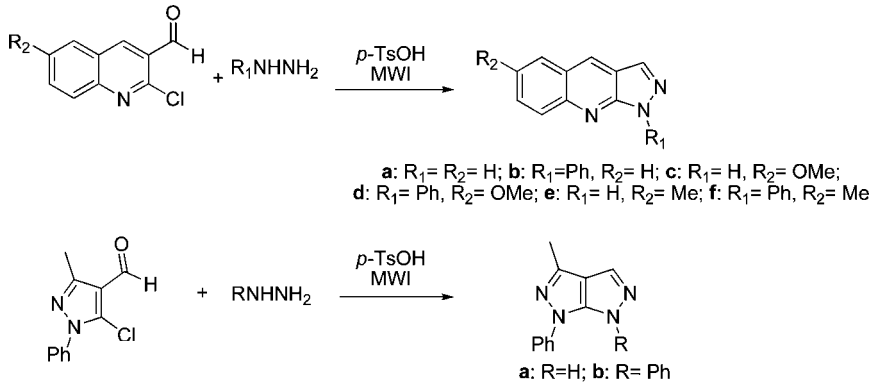
The developed methodology was applied in the synthesis of different pyrazoles as summarized in Table 43. Interestingly all alkynes with a carbonyl group in a neighboring position reacted smoothly affording the desired products whereas the substrate phenylacetylene failed to give the desired pyrazole even in trace amounts (Table 43, entry 4). This requirement suggests the existence of coordination between $InCl_3$ and the carbonyl group, and this probably promotes the reaction by lowering the LUMO of the alkyne moiety.[398]

In a recent manuscript, Varma et al. reported the synthesis in water of several pyrazoles, pyrazolidines, and phthalazines. These heterocyclic structures were prepared through a microwave-assisted cyclocondensation of hydrazine derivatives with alkyl dihalides or ditosylates. The reactions were carried out in slightly alkaline conditions at 120 °C and MW power of 80−100 W, Table 44.[399]

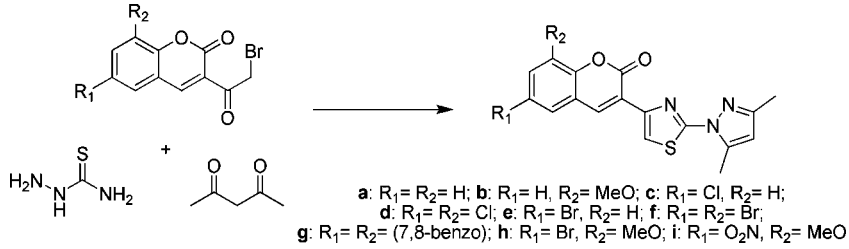
In the continuation of his work, Varma et al. reported the room temperature preparation of pyrazoles and diazepines in aqueous media. The condensation of hydrazines/hydrazides with several 1,3-diketones catalyzed by polystyrene supported sulfonic acid (PSSA) afforded the desired pyrazoles in good to excellent yields within 1−2 min (Table 45).[400]

Adib et al. reported, in a recent work, an efficient three-component reaction that leads to the preparation of important heterocycles designated by imidazo[1,2-*a*]pyridines and imidazo[1,2-*a*]thiazoles.[401] The reaction involves the combination of 2-aminopyridine, aldehydes, and isocyanides in water without the use of any catalyst (Scheme 85).

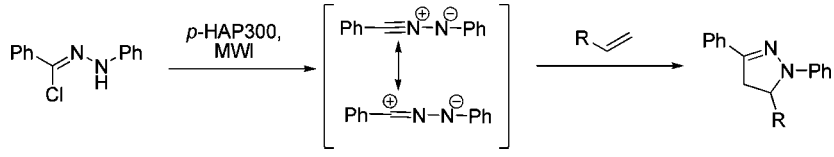
Scheme 77



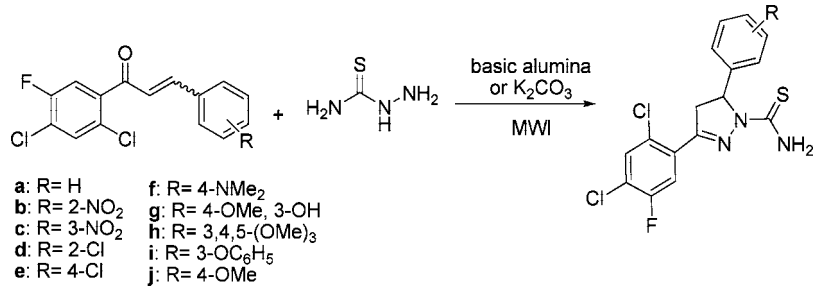
Scheme 78



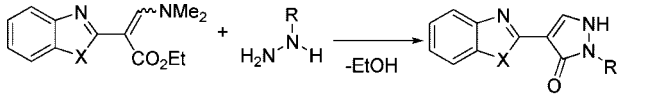
Scheme 79



Scheme 80

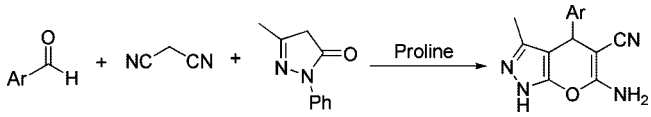


Scheme 81



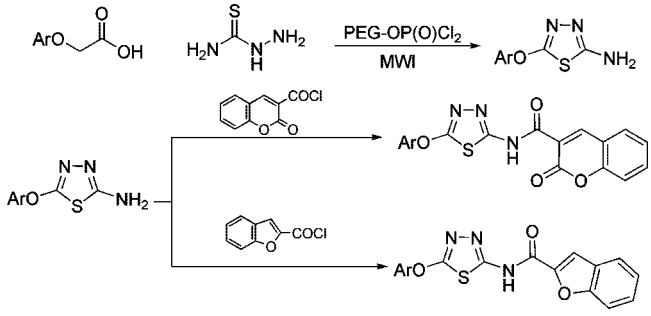
a: X= NH, R= Me, **b**: X= NH, R= Ph, **c**: X= O, R= Ph

Table 41

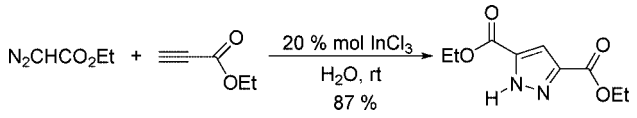


entry	Ar	yield (%)
1	C_6H_5	99
2	4-ClC_6H_4	96
3	3-ClC_6H_4	96
4	2-ClC_6H_4	95
5	4-$NO_2C_6H_4$	97
6	3-$NO_2C_6H_4$	98
7	4-BrC_6H_4	96
8	2,4-$Cl_2C_6H_4$	95
9	4-MeC_6H_4	90
10	4-OHC_6H_4	85
11	4-$MeOC_6H_4$	99

Scheme 82



Scheme 83



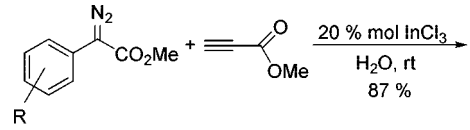
4.2.3. Reactions in PEG or PEG Tag Approaches

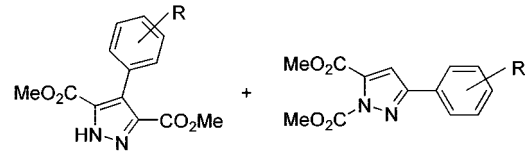
Sun et al. demonstrated that a polymer-supported diamine can be used as a versatile precursor for the construction of pharmacologically interesting bis-benzimidazoles through the use of commercially available building blocks (Scheme 86). The coupling of microwave technology with a liquid-phase synthesis strategy constitutes a novel and attractive avenue for the rapid generation of structurally diverse libraries. The desired heterocycles were prepared in good yields (>72%) and in good purity (71%).[402]

Sun and co-workers prepared a library of 2-alkylthiobenzimidazoles immobilized on MeO-PEG-OH polymers (MW = 5000) via liquid-phase synthesis.[403,404] Whenever it was necessary, the intermediates could be purified by polymer precipitation with diethyl ether. According to Scheme 87, the precursor benzimidazole could be straightforwardly prepared in four steps starting from commercially available starting materials. The desired 2-alkylthiobenzimidazole was then obtained by thio-alkylation in the presence of triethylamine. This last transformation provided the target molecules (after cleavage from the support) in 72−99% yield and in considerable purity (60−90%).

Sun et al. explored the possibility of expanding the scope of their protocol described above in order to prepare benzimidazoles.[405] After the key cyclization step of the produced diamine with triphosgene, benzimidazoles could be obtained in high yields (81−98%) and in high purity (84−96%) after hydrolysis from the support (Scheme 88).

Table 42





entry	diazo R	ratio A/B	A yield (%)	B yield (%)
1	H	91:9	82	7
2	*m*-MeO	92:8	81	8
3	*p*-MeO	94:6	90	4
4	*p*-F	89:11	80	10
5	*p*-Br	88:12	77	12
6	*p*-CF_3	86:14	83	9

Scheme 84

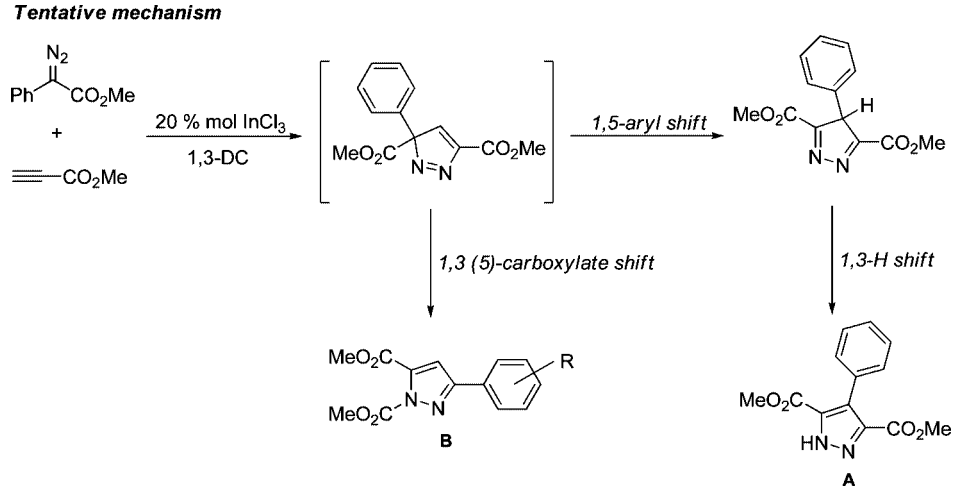
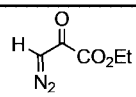
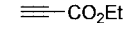
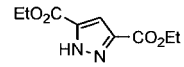
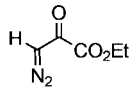
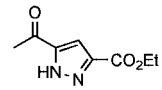
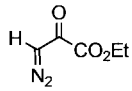
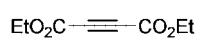
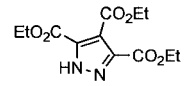
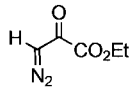
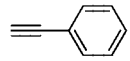
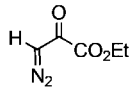
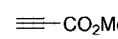
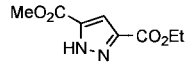
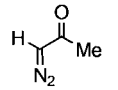
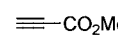
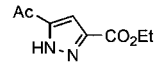
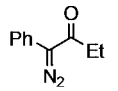
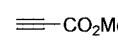
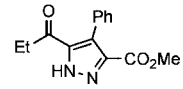
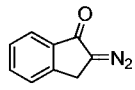
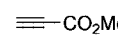
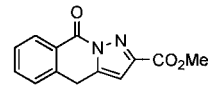
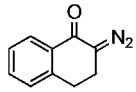
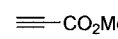
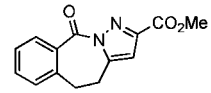
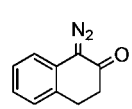
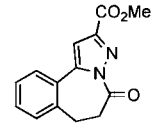
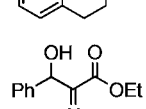
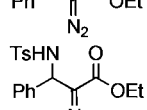
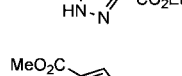
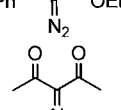


Table 43

Entry	Diazo	Alkyne	Product	Yield (%)
1				87
2				81
3				93
4			-	-
5				79
6				43
7				71
8				47
9				37
10				20
11				88
12				54
13			-	-

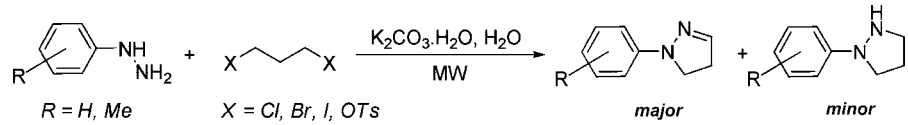
3,5-Pyrazolidinediones are a class of five-membered heterocyclic compounds bearing two nitrogens, which have been used clinically for treatment of rheumatoid arthritis and various other diseases. Due to some undesired side effects, Janda et al. focused their efforts on preparing a library of such compounds using polymer-supported chemistry (on PEG).[406] The key cyclization step between di-substituted malonic acids and methylhydrazine was accomplished in the presence of benzotriazol-1-yloxy-tripyrrolidinophosphonium hexafluorophosphate (PyBOP) in 98% yield (Scheme 89). Direct cyclization using malonic esters failed. Purification of the intermediates in this protocol required the precipitation of the polymer using isopropanol rather than diethyl ether. This is due to the presence of several polar byproducts that also precipitate with diethyl ether.

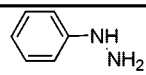
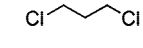
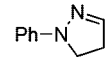
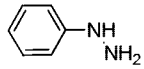
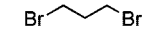
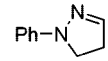
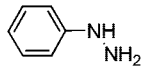
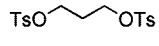
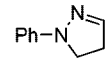
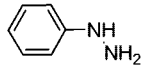
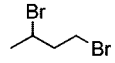
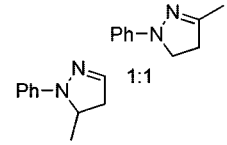
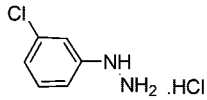
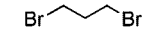
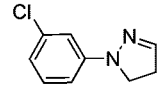
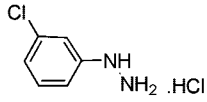
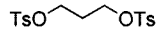
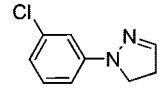
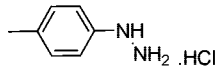
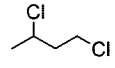
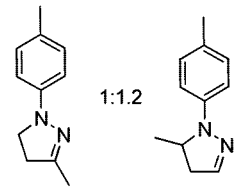
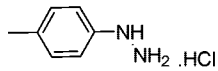
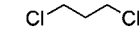
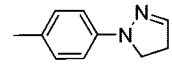
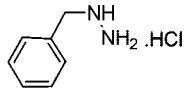
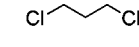
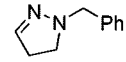
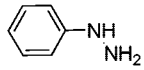
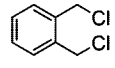
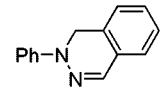
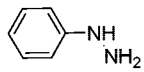
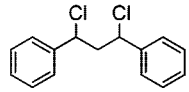
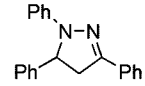
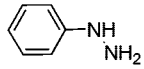
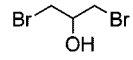
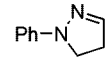
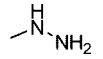
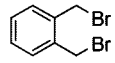
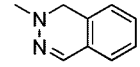
Pyrazoline moieties have a wide range of applications in agricultural pesticides and luminescent and fluorescent target molecules. Xia et al. accomplished their synthesis on a polymer support under microwave irradiation by cycloaddition of PEG-supported acrylates with nitrilimines.[407] The last were generated *in situ* by oxidation of phenylhydrazones with di(acetoxy)iodobenzene (Scheme 90). The cycloaddition was conducted under neat conditions, because the support melted under microwave irradiation, and proved to be strongly dependent on phenylhydrazone substitution pattern (being favored with electron-donating substituents).

Sun et al. developed a straightforward methodology to synthesize a library of 3,5-disubstituted thiohydantoins with medicinal value. The methodology depicted in Scheme 91, takes the advantage of combining microwave irradiation and polymer-soluble technologies to rapidly prepare a highly pure library. In the key step of this methodology, the heterocycle was formed with excellent yields (>90%) and high purity (81%) as it self-detaches from the support.[408] More recently, the methodology was extended to 1,3-substituted hydantoin with similar efficiency.[409]

1,3,4-Oxadiazole derivatives are a family of heterocycles with wide applications in medicinal chemistry. This family

Table 44

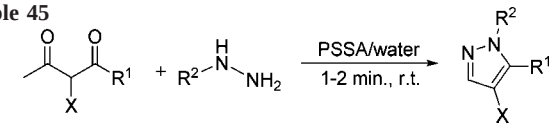


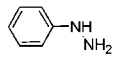
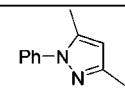
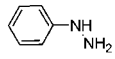
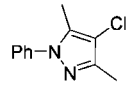
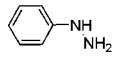
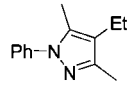
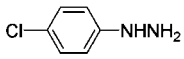
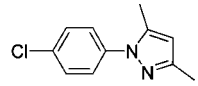
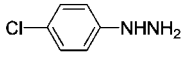
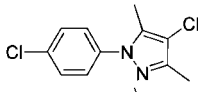
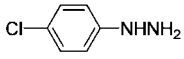
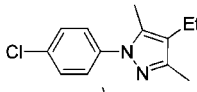
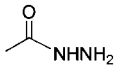
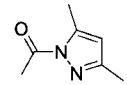
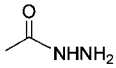
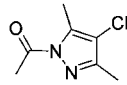
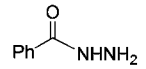
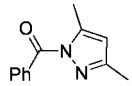
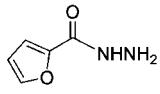
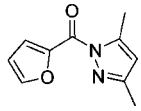
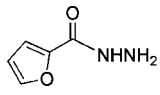
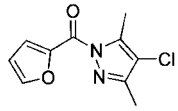
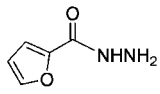
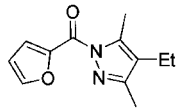
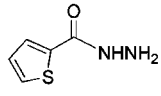
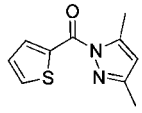
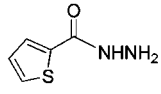
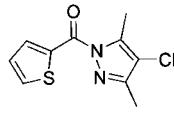
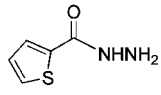
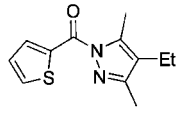
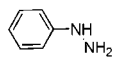
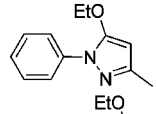
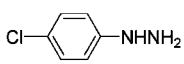
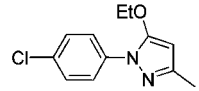
Entry	Hydrazine derivatives	Dihalides or ditosylates	Main products	Yield (%)
1				68
2				65
3				70
4			 1:1	65
5				64
6				66
7			 1:1.2	63
8				70
9				60
10				89
11				60
12				81
13				85
14	$H_2N\text{-}NH_2.H_2SO_4$			74
15	.2HCl			80
16	.2HCl			60

can be synthesized by several methodologies, in particular by condensation of diacylhydrazines in the presence of dehydration agents. Li et al. prepared these compounds using this latter methodology in the presence of PEG-supported dehydrating agent under solvent-free conditions in a microwave oven (Scheme 92).[410] This reaction required only a few minutes to achieve good yields (75−90%) under relatively mild conditions.

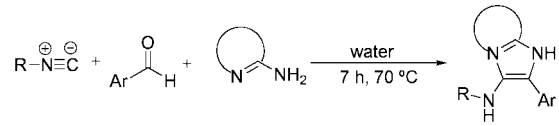
Another important family of heterocycles in medicinal chemistry, the 1,2,4-oxadiazolines, were also prepared using this methodology. The PEG-supported chlorinated hydroxylimines were cyclized with several imines in good yields

Table 45

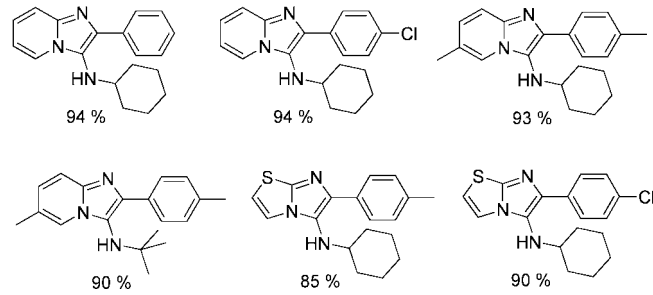


Entry	Hydrazine/ hydrazide	Diketone R^1	Diketone X	Products	Yield (%)
1		CH_3	H		92
2		CH_3	Cl		75
3		CH_3	Et		82
4		CH_3	H		85
5		CH_3	Cl		72
6		CH_3	Et		80
7		CH_3	H		90
8		CH_3	Cl		78
9		CH_3	H		90
10		CH_3	H		92
11		CH_3	Cl		85
12		CH_3	Et		88
13		CH_3	H		91
14		CH_3	Cl		85
15		CH_3	Et		80
16		OEt	H		85
17		OEt	H		80

Scheme 85



Selected examples



(>79%) and excellent levels of purity (>89%) to furnish a library of the desired heterocycles (Scheme 93).[411]

4.2.4. Reactions in Ionic Liquids

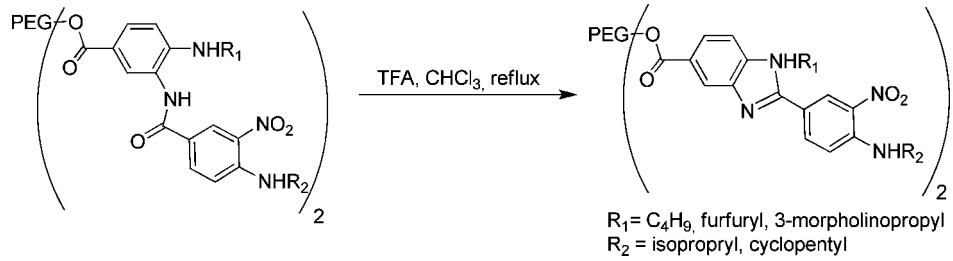
N-Heterocyclic carbene complexes of palladium are formed *in situ* using ionic liquids based on imidazolium ring systems.[412] The palladium carbene complexes are formed by the deprotonation of the imidazolium cation of [bmim][Br] in the presence of the catalyst precursor (Scheme 94).[413]

Several groups have studied Heck coupling in ionic liquids based on imidazolium or pyridinium cation structure using $PdCl_2$ or $Pd(OAc)_2-Ar_3Ph$ as catalyst and Et_3N or $NaHCO_3$ as base.[414,415]

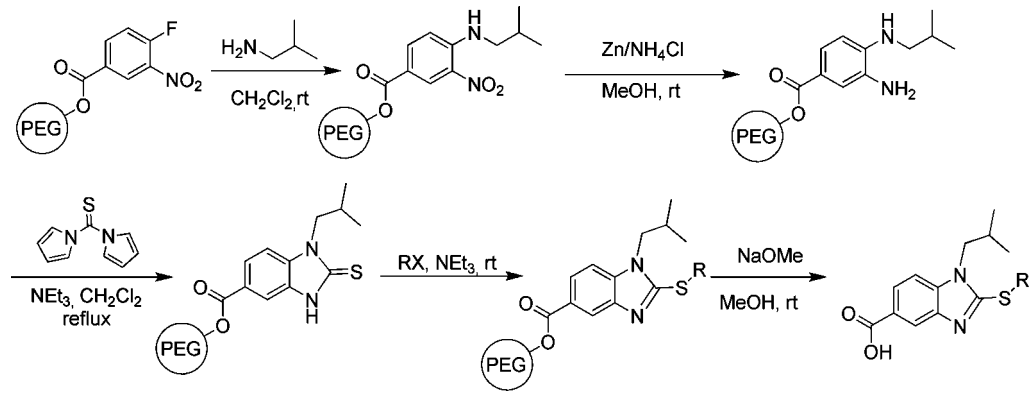
The high catalyst solubility in ionic liquids allowed the product isolation by extraction into nonpolar organic solvent. The higher catalytic activity observed for the reactions carried out in imidazolium ionic liquids compared with those in the pyridinium analogues has been attributed to the formation of palladium carbene complexes in the former ionic liquid. The Heck reaction with a ligand-less palladium catalyst has been reported in biphasic conditions using high melting alkylammonium tetrafluoroborate and water or toluene.[416] This method overcomes the solubility problem of the organic substrates and simplifies the separation of products and recycling of the reaction media.

Lin et al.[417] described a novel and highly efficient methodology for preparation of N-heterocycle derivatives with biological activity by Markovnikov's addition using ionic liquids. The Markovnikov addition is a useful method to prepare C−C, C−N, and C−S compounds using in general harsh bases, strong acids, or high temperature, which would lead to undesirable byproducts and other residues.[418,419] The authors discovered that the use of ILs as a recyclable reaction media, as well as an efficient catalyst, for Markovnikov's addition of N-heterocyclic compounds to vinyl esters affords the corresponding N-heterocycle derivatives in high yields under mild and neutral conditions (Table 46). The reactions performed in ILs containing BF_4 as anion exhibited excellent catalytic activity, while no reaction was observed in the case of ILs containing PF_6 as anion (entries 2 and 4). This observation was attributed to the poor solubility of some *N*-heterocyclic compounds in hydrophobic ionic liquids. ILs containing a longer cationic alkyl chain exhibited higher Markovnikov's addition activity. When the reaction was performed using 4-nitroimidazole and vinyl acetate in a solventless system, no product was observed after 4 days

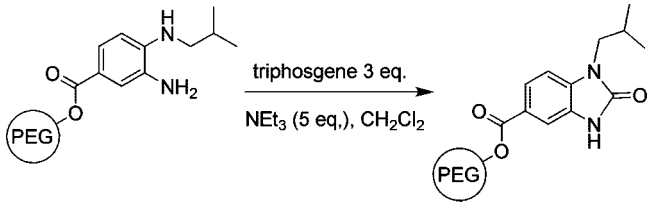
Scheme 86



Scheme 87



Scheme 88



due to the poor solubility of 4-nitroimidazole in vinyl acetate (entry 8), while in organic solvent such as DMSO only 0.3% of desirable product was formed even after 4 days (entry 9). All the reactions proceeded smoothly in IL [bmim][BF_4] without any other catalyst required.

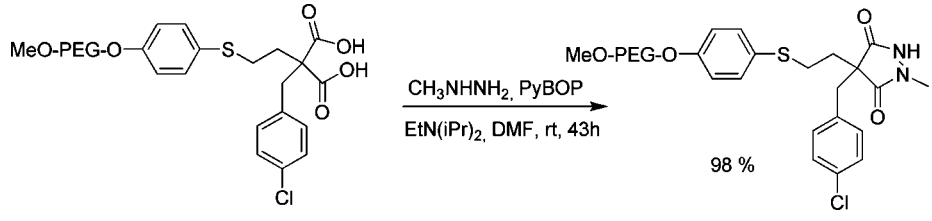
The structure of the N-heterocycle selected also affected the results of Markovnikov's addition reaction with a reactivity reducing in agreement with their nucleophilicity: 4-nitroimidazole < imidazole < 4-methylimidazole. Additionally the IL [bmim][BF_4] could be recovered and recycled five times without loss of activity in the case of Markovnikov's addition of imidazole with vinyl acetate. Apart from imidazole derivatives, other N-heterocycles such as pyrazole, triazole, and pyrrole also presented high Markovnikov's addition activity.

More recently, the same authors described a basic ionic liquid, [bmim][OH], as an efficient catalyst and alternative reaction media for the Markovnikov addition of N-heterocycles to vinyl esters without the requirement for any other catalyst or organic solvent.[420]

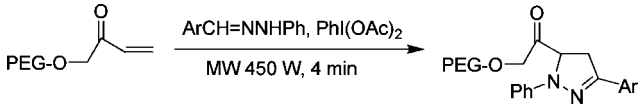
The basic IL [bmim][OH] has been applied to catalyze the Michael addition of active methylene compounds to carboxylic esters, nitriles, and conjugate ketones,[421] but the catalytic mechanism involving this IL was ambiguous. First, the authors studied the Markovnikov addition of 4-nitroimidazole to vinyl acetate (4 equiv) at 50 °C in IL [bmim][OH][422] for 2 h, and a single product was prepared in 93% isolated yield (no byproducts resulting from anti-Markovnikov addition, hydrolytic, acylation, or other reactions were observed). This procedure was extended to several imidazoles and vinyl esters without the use of any other catalyst affording the corresponding imidazole derivatives in moderate to high yields (73−93%) **(**Table 47**)**. The IL remained intact after subsequent cycles without any problem, while it was observed that this reaction did not proceed in some organic solvents such as THF, DMSO, and DMF. Other five-membered N-heterocycles such as pyrrole, pyrazole, and triazole also presented high Markovnikov addition activity.

The catalytic mechanism for the Markovnikov addition reaction promoted by [bmim][OH] was postulated and supported by experimental data. Owing to the electron-withdrawing effect of the carboxylic group, the α-carbon of the vinyl group carries partial positive charge. When the substrate was added, the hydroxyl anion deprived the N-proton and the nucleophile simultaneously added to the partial positively charged α-C position. The resulting negative charge at the β-C carbon could be stabilized by C2−H of [bmim][OH], and then the water formed would deliver the proton to form the Markovnikov adduct (Scheme 95).

Scheme 89



Scheme 90

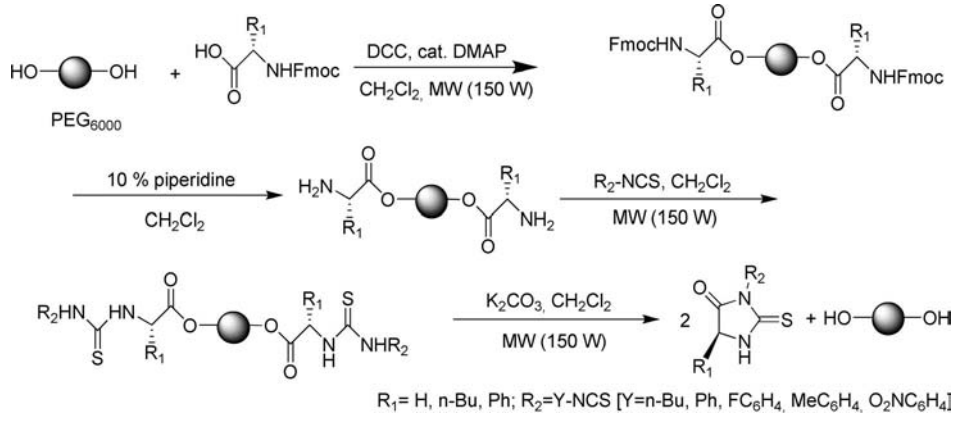


Two pieces of evidence from ^{13}C NMR spectroscopy supported this proposed mechanism: (a) comparison of the ^{13}C NMR spectra of imidazole (neat) with a mixture of imidazole and 1 equiv of IL [bmim][OH] showed an upfield shift of C2 (0.27 ppm) and C4 (0.55 ppm) of imidazole in the mixture, indicating the deprivation of the N-proton of imidazole by the hydroxyl anion of [bmim][OH]; (b) comparison of the ^{13}C NMR spectra of butyrate (neat) with a mixture of butyrate and 1 equiv of IL [bmim][OH] showed an upfield shift of 0.13 ppm for the carbonyl carbon indicating the existence of a hydrogen bond of the imidazolium cation with the vinyl ester.

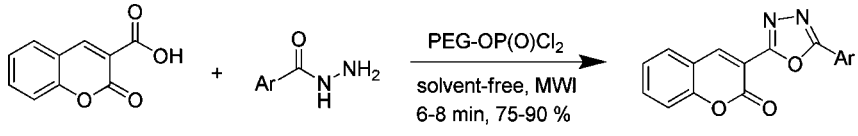
Bao and co-workers[423] described the Ulmann-type coupling reaction of vinyl bromides and imidazoles in ILs providing the corresponding *N*-vinylimidazoles in good to excellent yields by using L-proline as the ligand. *N*-Vinylimidazoles have been applied as building blocks for the synthesis of metal complexes and also as important intermediates in the synthesis of several heterocycles.[424−426]

Normally, their preparation involves direct addition of imidazoles to alkynes,[427] olefination of β-hydroxyimidazoles,[428,429] N-vinylation of imidazole with vinyl halides or acetates,[430] and copper-catalyzed C−N bond cross-coupling with vinylboronic acid.[431] All of these protocols suffer from either harsh reaction conditions or lack of stereocontrol of double bond geometry. First, the authors prepared *N*-styrylimidazole in 80% of yield using the IL [bmim][BF_4] by coupling bromostyrene and imidazole in the presence of 10 mol % CuI, 20 mol % L-proline, and K_2CO_3 (Table 48).Without the addition of L-proline, the reaction gave only 9% yield under the same conditions. This methodology was studied with several vinyl bromides and different imidazoles giving the desired coupling products in good to excellent yields (75−93%). Another important advantage was the possibility to recycle and re-use the CuI/L-proline/IL at least four times with a small effect on the rate or yield of the reaction during each cycle.

Scheme 91



Scheme 92



Rahmati et al.[432] reported a new efficient procedure for the synthesis of trisubstituted imidazoles from an one-pot condensation of 1,2-diketone or hydroxyketone and aldehyde and NH_4OAc in the IL 1,1,3,3,-*N*,*N*,*N*′,*N*′-tetramethylguanidinium trifluoroacetate [TMG][TFA] at 100 °C.

Using IL tetramethylguanidinium [TMG] cation as promoter and solvent for the preparation of multisubstituted imidazoles represents a significant improvement (15−40 min in IL, 100 °C, 81−94% of yield) over conventional thermal heating.[433,434] Additionally, the reaction times are also comparable to the ones obtained by microwave irradiation (20 min in HOAc, 180−200 °C) (Scheme 96).[435,436] According to the authors, the solvophobic interaction behavior of IL guanidinium generates an internal pressure, which promotes the association of the reactants in the solvent cavity and would justify the lower reaction times. The authors extended the reaction of 1,2-diketo with several aromatic aldehydes carrying either electron-releasing or electron-withdrawing substituents in the *para* positions.[432] The IL [TMG][TFA] tested was easily separated from the reaction medium by washing with water and evaporating the solvent under vacuum and reused it for subsequent cycles without any loss of efficiency.

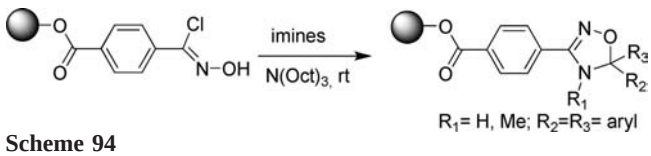
4.2.5. Reactions in Fluorinated Fluids

Zhang et al. described the preparation of a range of hydantoins and thiohydantoins in 85−95% purity by reaction of fluorous L-α-amino esters with isocyanates or thioisocyanates followed by removal of fluorous alcohol and triethylamine and the salt using fluorous silica gel and acidic ion-exchange resin (Amberlite G-50) (Scheme 97).[437]

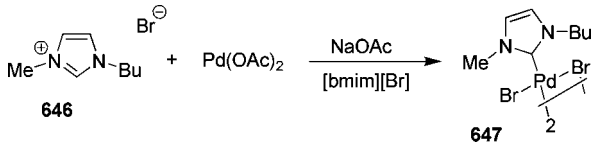
Zhang et al. also explored the use of perfluorooctylsulfonyl group as a fluorous tag for the synthesis of trisubstituted hydantoins. The fluorous tag was removed by microwave-assisted deoxygenation catalyzed by Pd(dppf)Cl_2 (5 mol %). Both the α-amino ester and hydantoins were purified by F-SPE (Scheme 98).[438]

Zhang and Tempest extended the combination of fluorous tags and microwave irradiation to multicomponent reactions such as for synthesis of quinoxalinones and benzimidazoles by Ugi/de-Boc/cyclization sequence. The authors combined

Scheme 93



Scheme 94



the use of a fluorous-Boc group component as the limiting agent and F-SPE for purification of the intermediate precursor containing the fluorous tag and non-fluorous product by elution with MeOH and MeOH/H_2O (80:20), respectively (Scheme 99).[439]

Curran et al. prepared several hydantoins by cyclization under microwave conditions followed by separation using F-SPE in order to remove the fluorous benzyl alcohol (Table 49).[440]

Zhang extended the use of 1*H*,1*H*,2*H*,2*H*-perfluoro-decanethiol as a fluorous tag for the synthesis of disubstituted pyrimidones from 2,4-dichloro-6-methylpyrimidine by attaching the fluorous tag, substitution with 3-(trifluoromethyl)pyrazole, thioether oxidation, and tag displacement with amines or thiols. Again, the intermediates as well the final pyrimidines were purified by F-SPE (Scheme 100).[441]

4.3. Containing Three Nitrogen Atoms

4.3.1. Solvent-Free Reactions

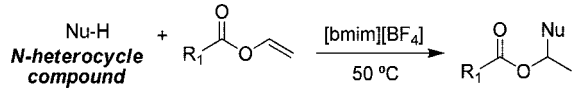
The method most applied to the synthesis of 1,2,3-triazoles in conventional organic synthesis is based on cycloadditions. Under solvent-free conditions, there are several methods to achieve this family of compounds with most of them also being based on cycloaddition reactions. Similar to the classic methods, *C*-carbamoyl-1,2,3-triazoles can be obtained under MWI through a 1,3-dipolar cycloaddition of azides with acetylenic amides. Despite the good to moderate yields, this method has proven to have rather low regioselectivity.[442] Recently, NHC-containing copper complexes (NHC = N-heterocyclic carbene) were reported as efficient catalysts for 1,3-dipolar cycloaddition between azides and several alkynes (unactivated and activated alkynes) in the solvent-free reaction at 45 °C,[443] while CuI was reported to be effective in the microwave version of the same reaction,[444] From the reaction of dipole α-azidomethylphosphonate with alkynes, *β*-functionalized alkyltriazoles can be obtained in good yields through the use of a microwave oven (Scheme 101). Despite the better yields obtained in MWI than in conventional heating, the use of enamines instead of the prior alkynes proved to be more efficient in conventional heating conditions. This way, better regioselectivities were obtained, while the use of toluene as solvent decreased the reaction efficiency.[445]

Triazoles can also be synthesized through the cycloaddition of azides with the readily available enol ethers. Despite the severe reaction conditions (200 °C), 1,2,3-triazoles can be obtained in modest to good yields under conventional heating, as can ring-fused triazoles.[446]

Through the cycloaddition of 2-aryl-cyano- or 2-aryl-carbethoxy-1-nitroethenes with trimethylsilyl azide, 4-aryl-1*H*-1,2,3-triazoles can be efficiently prepared under conventional heating using tetrabutylammonium fluoride (TBAF) as a catalyst (10 mol %) (Scheme 102). Milder conditions are needed when cyano nitroethene is used (30 °C, 3h); however carbethoxy nitroethenes had also proven to be very efficient despite the need to use harsher conditions (50−80 °C, 4−12 h).[447] This organic catalyst has been also successfully applied to the cycloaddition of 3-nitrocoumarins with $TMSN_3$ for the synthesis of chromeno[3,4-*d*][1,2,3]triazol-4(3*H*)-ones.[448]

The substitution of the ethoxy moiety in aminopyrazole-carbonylhydrazides with an amine under SFC and conventional heating (150 °C, 3 h) proved to be an efficient method to obtain pyrazolyl-substituted 1,2,4-triazoles in moderate to good yields (Scheme 103).[449] Recently, 4-amino-5-methyl-3-thioxo-2*H*-1,2,4-triazole was reported to react with aldehydes under microwave irradiation to yield the corresponding

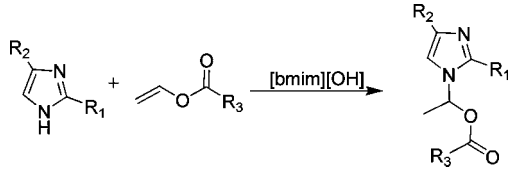
Table 46



entry	Nu-H	solvent	R_1	vinyl ester (equiv)	time (h)	yield (%)
1	4-nitro-IM	[bmim][BF_4]	CH_3	6	12	98
2		[bmim][PF_6]	CH_3	6	48	*a*
3		[emim][BF_4]	CH_3	6	48	96
4		[emim][PF_6]	CH_3	6	48	*a*
5		[bmim][BF_4]	CH_3	4	24	95
6		[bmim][BF_4]	CH_3	2	48	96
7		[bmim][BF_4]	CH_3	6	96	97
8		Solventless	CH_3		96	*a*
9		DMSO	CH_3	6	96	0.3
10		[bmim][BF_4]	$CH_3(CH_2)_3$	6	48	90
11		[bmim][BF_4]	$(CH_3)_2CH$	6	48	86
12		[bmim][BF_4]	$CH_3(CH_2)_6$	6	72	91
13		[bmim][BF_4]	CH_2=$CHO_2C(CH_2)_2$	6	72	89
14		[bmim][BF_4]	CH_2=$CHO_2C(CH_2)_4$	6	36	93
15		[bmim][BF_4]	Ph	6	60	94
16		[bmim][BF_4]	CH_3	6	48	92
17	IM	[bmim][BF_4]	CH_2=$CHO_2C(CH_2)_2$	6	24	97
18		[bmim][BF_4]	CH_3	6	48	93
19	4-Me-IM	[bmim][BF_4]	CH_3	6	72	97

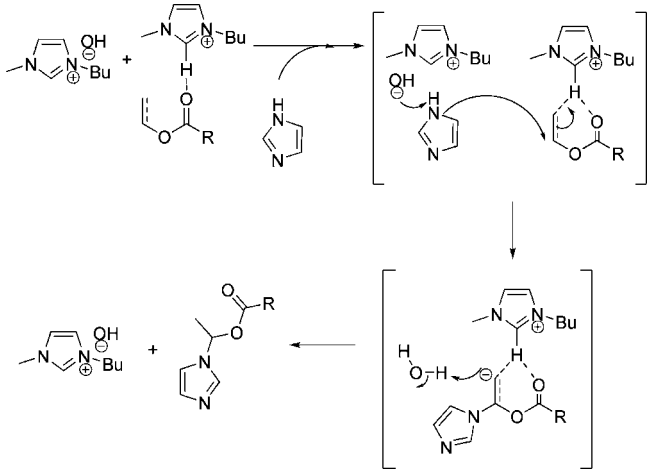
[a] Not determined.

Table 47



entry	R_1	R_2	R_3	time (h)	yield (%)
1	H	NO_2	CH_3	2	93
2	H	NO_2	$CH_3(CH_2)_2$	8	82
3	H	NO_2	$(CH_3)_2CH$	8	75
4	H	NO_2	$CH_3(CH_2)_3$	12	79
5	H	NO_2	$CH_3(CH_2)_4$	12	76
6	H	NO_2	Ph	12	81
7	H	H	CH_3	4	91
8	H	H	$CH_3(CH_2)_2$	8	80
9	H	H	$CH_3(CH_2)_4$	12	78
10	H	H	Ph	12	84
11	H	CH_3	CH_3	4	88
12	CH_3	H	CH_3	4	73
13	CH_3	NO_2	CH_3	12	85

Scheme 95



imine in good yields (77−86%), which can be easily converted to other 1,2,4-triazole derivatives.[450]

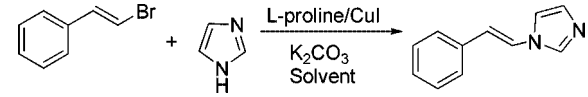
1,2,4-Triazoles can also be efficiently prepared under SFC at room temperature through oxidative transformation of arenecarbaldehyde 3-methylquinoxalin-2-yl-hydrazones to 1-aryl-4-methyl-1,2,4-triazolo[4,3-*a*]quinoxalines with iodobenzene diacetate (Scheme 104).[451]

Using acidic alumina as supporting material, thiadiazolyl-substituted triazoles can be prepared in good to excellent yields through microwave irradiation of 2-aminothiadiazoles and 5-alkyl-2-mercapto-1,3,4-oxadiazoles (Table 50).[397]

Triazole derivatives, triazolinediones, can be obtained in good yields through oxidation of urazoles with potassium dichromate in the presence of aluminium chloride at room temperature under solvent-free conditions.[452] Mild and heterogeneous oxidation of urazoles to their corresponding triazolinediones via *in situ* generation of Cl^+ using a silica sulfuric acid/$KClO_3$ or a silica chloride/oxone system was recently reported.[453]

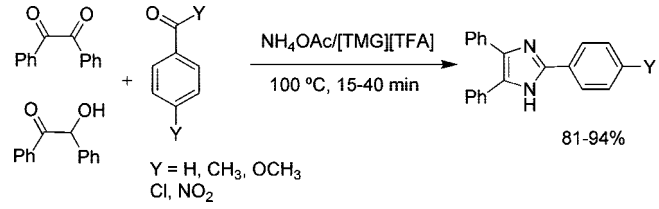
A simple, one-pot pathway for the preparation of 4-substituted phenyl derivatives of urazoles, starting from aniline derivatives and after reaction with ethyl chloroformate, was reported. The corresponding carbamate derivatives obtained were reacted with ethyl carbazide to yield the desired urazoles.[454]

Table 48

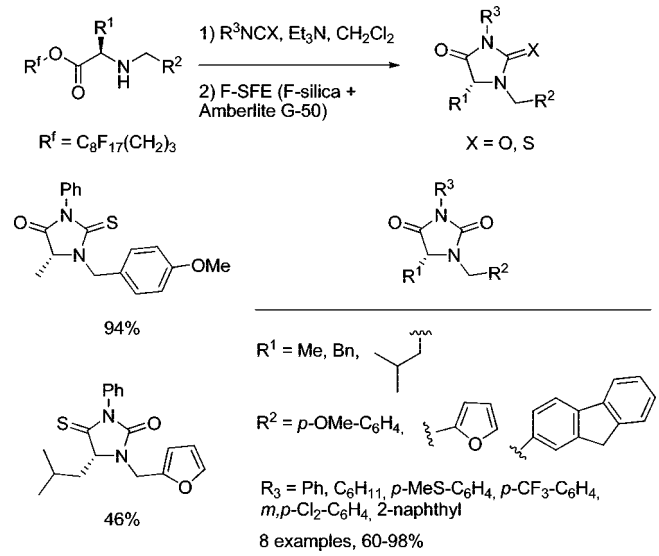


entry	solvent	temp (° C)	time (h)	yield (%)
1	[bmim][BF_4]	90	30	80
2	[bmim][BF_4]	110	20	87 (1st cycle) 85 (2nd cycle) 82 (3rd cycle) 83 (4th cycle)
3	[bmim][BF_4]	110	20	9
4	[bmim][PF_6]	110	20	70
5	[bmim][Br]	110	30	78
6	[bmim][I]	110	30	60
7	MeCN	reflux	36	25
8	DMSO	110	30	
9	DMF	110	30	
10	[Bpy][BF_4]	110	20	85

Scheme 96



Scheme 97

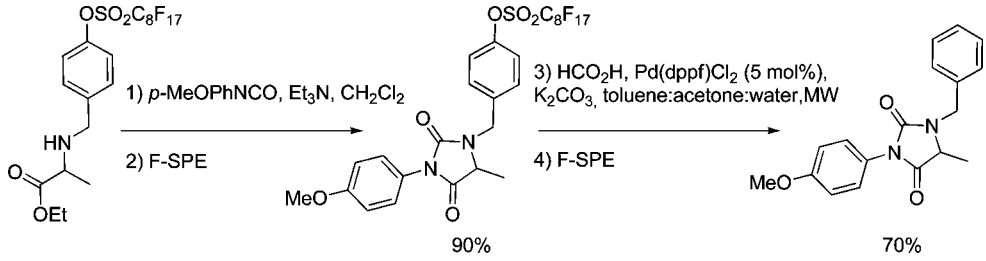


4.3.2. Reactions in Aqueous Media

In recent times, "click chemistry" has emerged as an important field of truly sustainable chemical transformations. Transformations classified as "click reactions" require only benign reaction conditions and simple workup and purification procedures, though they can still create molecular diversity with remarkable efficiency.[455]

Perhaps the most powerful "click" reaction described to date is the Cu(I)-catalyzed azide−alkyne cycloaddition,[456,457] a catalyzed variant of the Huisgen 1,3-dipolar cycloaddition to afford 1,2,3-triazoles.[458−460] The Cu(I)-catalyzed union of terminal alkynes and organic azides to give 1,4-disubstituted 1,2,3-triazoles exhibits remarkably broad scope and exquisite selectivity. The reaction performs best in aqueous systems, succeeds in a broad temperature range (0−160 °C), and is reasonably tolerant to pH values although the optimal pH is usually in the range of 7−9.

Scheme 98



Scheme 99

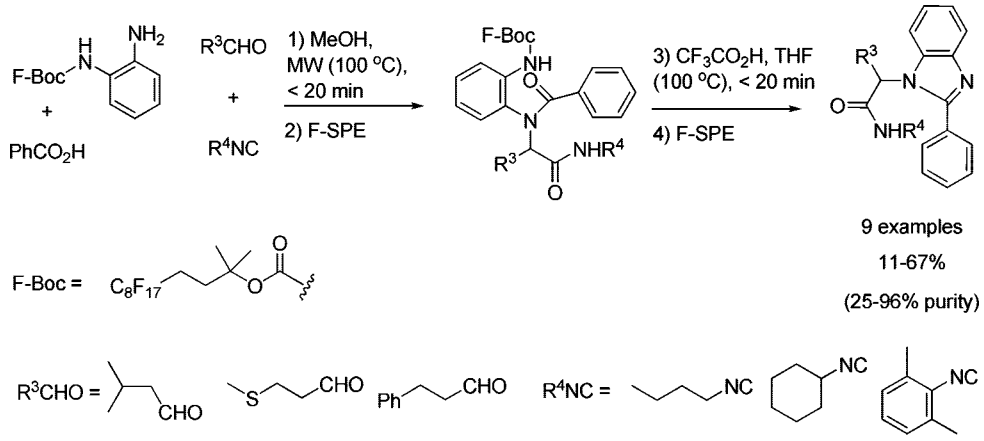
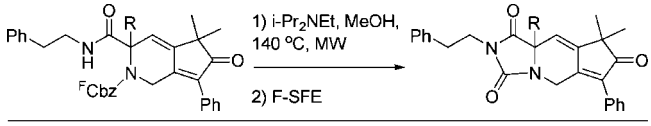


Table 49



R	yield (%)	purity (%)
Bn	90	86
p-F-Bn	99	85
m-CF_3−Bn	86	87

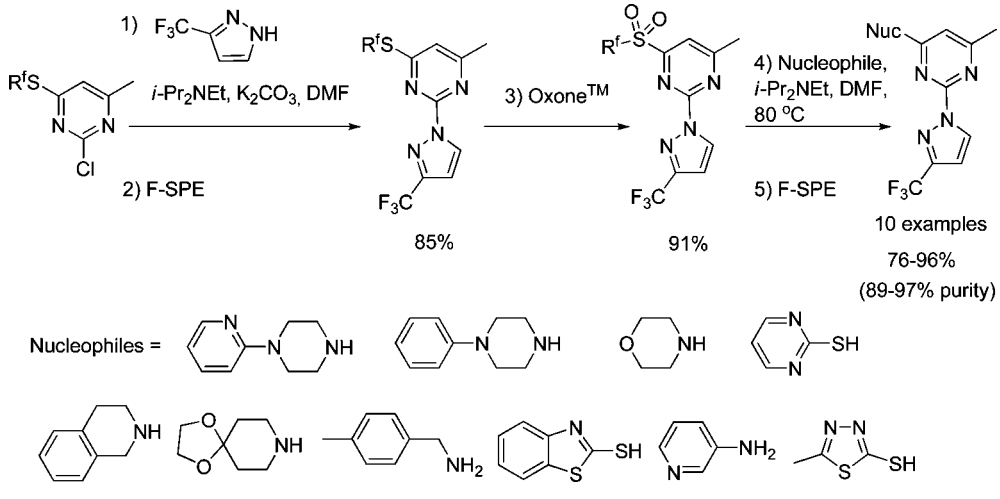
This topic in itself deserves a rather long and comprehensive bibliographic survey; therefore in this section, only some examples are presented.

Sharpless et al. have devoted considerable attention to this particular reaction, establishing it as an extremely useful methodology in a multitude of applications.[461] In Table 51, the preparation of 1,4-disubstituted 1,2,3-triazoles is shown.[462]

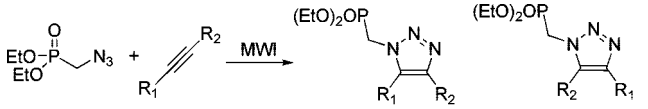
The mechanism proposed based on DFT calculations exhibits a strong correlation with the experimental evidence. The sequence starts with the coordination of the alkyne to the Cu(I) species leading to the formation of acetylide, followed by azide coordination to the copper atom by the nitrogen proximal to carbon. After this, the azide distal nitrogen attacks the C-2 carbon of the acetylide forming a six-membered copper(III) metallacycle. Ring contraction followed by proteolysis completes the proposed cycle affording the desired 1,2,3-triazoles (Scheme 105).[462]

Recently, Nolan et al. disclosed a new copper catalyst for the Huisgen cycloaddition reaction. In the presence of [(NHC)CuBr] complex, 1,2,3-triazoles were obtained in extremely high reaction rates and yields.[463] Different NHC ligands were evaluated, and saturated SIMes (SIMes = *N*,*N*′-bis(2,4,6-trimethylphenyl-(4,5-dihydro-imidazol-2-ylidene) proved to be the most efficient. Another interesting observation is related to the acceleration effect that occurred when

Scheme 100

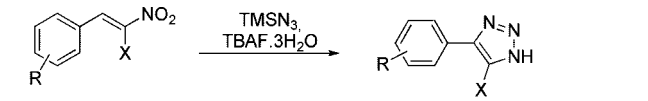


Scheme 101



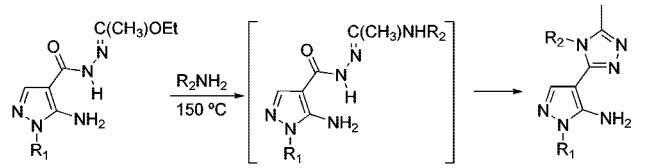
a: R_1= Me, R_2= $PO(OEt)_2$, **b**: R_1= H, R_2= CO_2Et,
c: R_1= Ph, R_2= CO_2Et, **d**: R_1= H, R_2= Ph, **e**: R_1= H, R_2= CH_2OH

Scheme 102



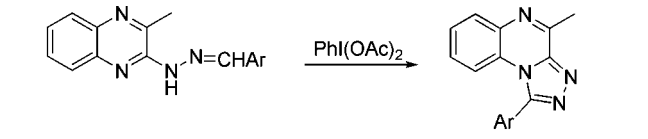
a: X= CN, R= H
b: X= CN, R= 4-Cl
c: X= CN, R= 4-MeO
d: X= CN, R= 4-OH
e: X= CN, R= 3,4-CH_2O_2
f: X= CO_2Et, R= H
g: X= CO_2Et, R= 4-Cl
h: X= CO_2Et, R= 3-O_2N
i: X= CO_2Et, R= 4-F_3C
j: X= CO_2Et, R= 4-NC
k: X= CO_2Et, R= 4-MeO
l: X= CO_2Et, R= 2-MeO
m: X= CO_2Et, R= 3-MeO
n: X= CO_2Et, R= 3,4-$(MeO)_2$

Scheme 103



a: R_1= Me, R_2= Ph
b: R_1= Me, R_2= 4-ClC_6H_4
c: R_1= Me, R_2= 4-$MeOC_6H_4$
d: R_1= Me, R_2= Bn
e: R_1= Me, R_2= $Ph(CH_2)_2$
f: R_1= Me, R_2= $Me_2N(CH_2)_3$
g: R_1= R_2= Ph
h: R_1= Ph, R_2= 4-ClC_6H_4
i: R_1= Ph, R_2= 4-$MeOC_6H_4$
j: R_1= Ph, R_2=Bn
k: R_1= Ph, R_2= $Ph(CH_2)_2$
l: R_1= Ph, R_2= $Me_2N(CH_2)_3$

Scheme 104



a: Ar= Ph, **b**: Ar= 4-MeC_6H_4, **c**: Ar= 4-ClC_6H_4, **d**: Ar= 4-$MeOC_6H_4$,
e: 3-$MeOC_6H_4$, **f**: Ar= 4-$(Me_2N)C_6H_4$

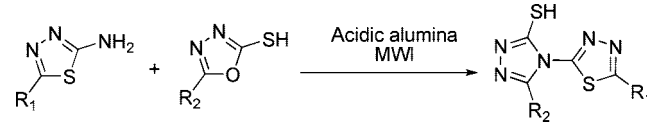
a bromide replaced the chloride on the complex (Table 52).[463] On the basis of the most successful catalytic system [(SIMes)CuBr], the authors presented an interesting method to prepare 1,2,3-triazoles in water, with organic azides generated *in situ* from the corresponding alkyl halides and sodium azide (Table 53).[463]

The general usefulness of this protocol was once again highlighted by the work of Liang et al., which rapidly accessed (1-substituted-1*H*-1,2,3-triazol-4-ylmethyl)-dialkylamines via a three-component reaction in water at room temperature (Scheme 106). Though the reaction allowed the presence of a variety of substituents, it is highly dependent on both electronic and steric effects.[460]

4.3.3. Reactions in PEG or PEG Tag Approaches

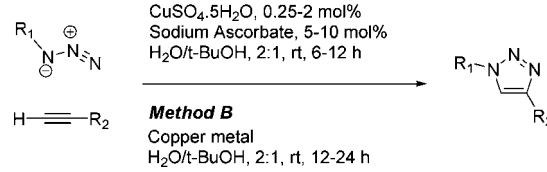
1,2,4-Triazoles are heterocycles with important applications as biologically active molecules, because they have the ability to replace amide bonds in peptides. This type of heterocycle was prepared in high purity using liquid-phase synthesis with the aid of a soluble polymeric support (PEG_{6000}) that could be recovered by precipitation with diethyl ether at the end of each reaction step.[464] The cyclization step that furnished the heterocycle was conducted between tri-substituted thioureas and arylacyl hydrazines in the presence of mercury salts (Scheme 107). In the last step, the polymeric support was removed with trifluoroacetic acid. Unfortunately, this methodology failed to give triazoles containing aryl substituents due to steric hydrance.

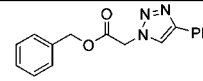
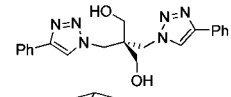
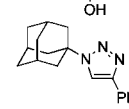
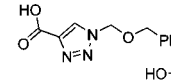
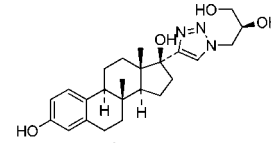
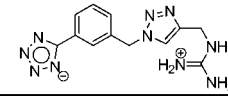
Table 50



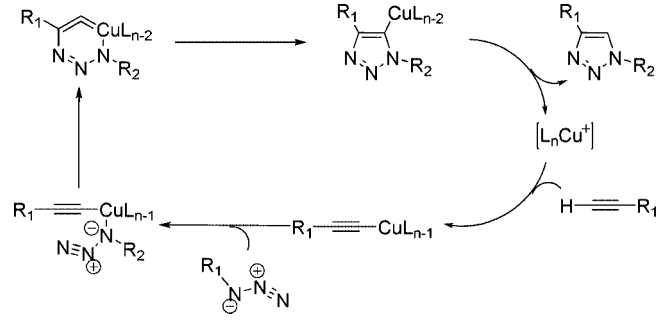
entry	R_1	R_2	reaction time (s)	yield (%)
1	Me	C_7H_{15}	80	92
2	Me	C_9H_{19}	60	93
3	Me	$C_{11}H_{23}$	80	92
4	C_7H_{15}	C_7H_{15}	60	89
5	C_7H_{15}	C_9H_{19}	40	93
6	C_7H_{15}	$C_{11}H_{23}$	80	86
7	C_9H_{19}	C_7H_{15}	40	87
8	C_9H_{19}	C_9H_{19}	80	79
9	C_9H_{19}	$C_{11}H_{23}$	60	77
10	$C_{11}H_{23}$	C_7H_{15}	60	83
11	$C_{11}H_{23}$	C_9H_{19}	80	89
12	$C_{11}H_{23}$	$C_{11}H_{23}$	40	83

Table 51



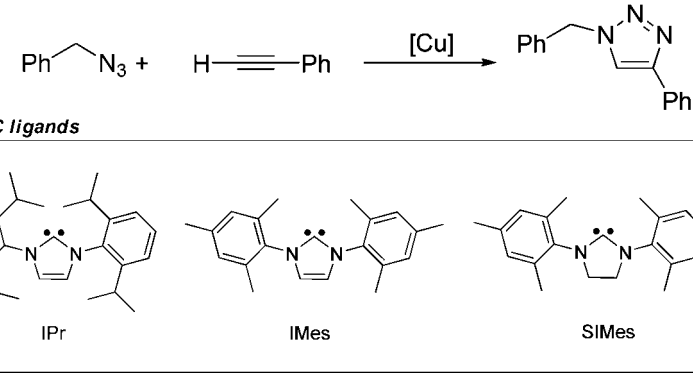
Entry	Method	Product	Yield (%)
1	**A**		92
2	**B**		98
3	**A**		84
4	**B**		88
5	**A**		94
6	**B**		88

Scheme 105



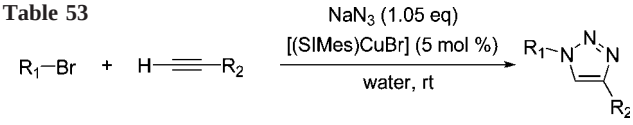
Dehydrogenation products of triazoles (4,5-dihydro-1,2,4-triazoles) have several applications related to their spectroscopic properties, which require high levels of purity. Wang et al. performed their synthesis using soluble polymer supported synthesis in order to achieve such a goal (Scheme

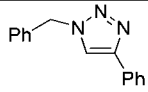
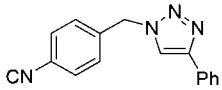
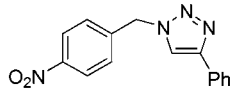
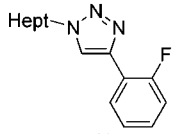
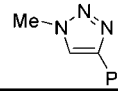
Table 52



entry	[Cu] (mol %)	solvent (mL)	*t* (h)	yield (%)
1	[(IPr)CuCl] (5)	water/*t*-BuOH (3)	18	18
2	[(IMes)CuCl] (5)	water/*t*-BuOH (3)	18	65
3	[(SIMes)CuCl] (5)	water/*t*-BuOH (3)	18	93
4	[(SIMes)CuBr] (5)	water/*t*-BuOH (3)	9	95
5	[(SIMes)CuBr] (5)	water (1)	0.5	98
6	[(SIMes)CuBr] (0.8)	neat	0.3	98
7	[CuBr]	neat	1	0

Table 53



Entry	*t* (h)	Product	Yield (%)
1	0.3		94
2	2.0		97
3	1.5		98
4	0.5		92
5	2.0		90

108). In the key cyclization step, PEG-supported chlorinate hydrazones were coupled with several imines to furnish the desired heterocycles in high yields (>75%) and high purity (>75%).[465]

4.3.4. Reactions in Fluorinated Fluids

A flourous version of azide click chemistry through the employment of the F-SPE approch has been used by Soós et al. for the cycloaddition between terminal alkynes and fluorous azides (Scheme 109). 1,2,3-Triazoles were obtained in excellent yields under mild conditions (room temperature overnight), and the procedure was further applied to the preparation of a cinchonidine alkaloid.[466]

4.4. Containing Four Nitrogen Atoms

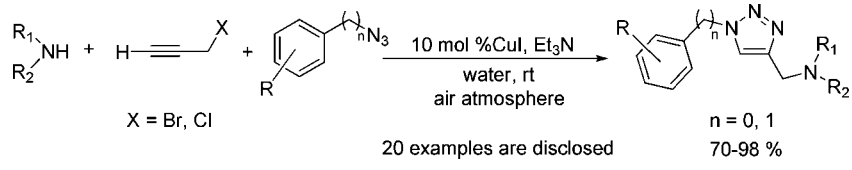
4.4.1. Solvent-Free Reactions

The preparation of 5-substituted-1*H*-tetrazoles can be efficiently achieved through the use of TBAF in cycloaddition reaction of nitriles with $TMSN_3$ in SFC (Scheme 110). The reaction conditions are not unique and a process optimization should be made depending on the substrate to be used. In the reported literature, temperature conditions such as 50−120 °C are used, and the reaction times may vary between 1 and 48 h.[467] In contrast, 1,5-fused tetrazoles can be prepared by simple grinding of a cyclic ketone with 4 equiv of sodium azide in presence of aluminium chloride at 50 °C for short reaction times (10−15 min).[468]

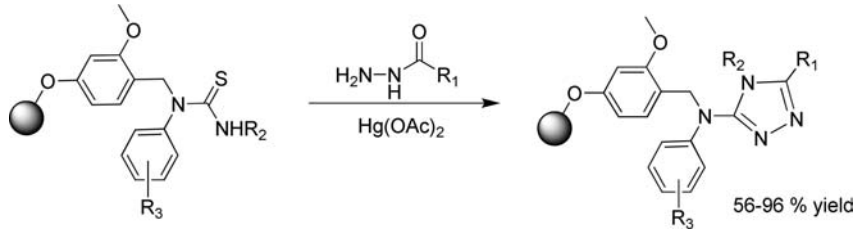
4.4.2. Reactions in Aqueous Media

In recent times, tetrazole functionality was reported as an important unit for coordination and medicinal chemistry, as well as in material sciences. The convenience of water as solvent was then again clearly demonstrated by Sharpless et al. in the preparation of 5-substituted 1*H*-tetrazoles. These important units were prepared, in a rather efficient way, from nitriles and sodium azide in the presence of a zinc salt (Table 54).[469] The use of water as solvent in the preparation of tetrazoles has another clear advantage because it diminishes the explosion hazard associated with endergonic groups such as aromatic azides and nitro compounds due to its high heat capacity. For instance, aqueous sodium azide solution is very stable at reflux temperatures.[469]

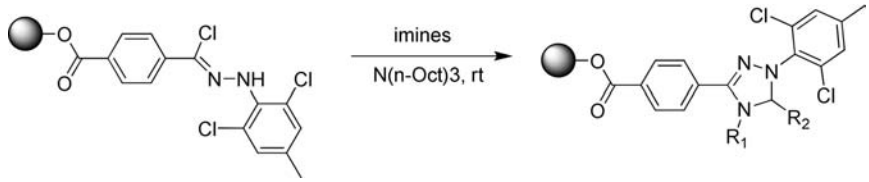
Scheme 106



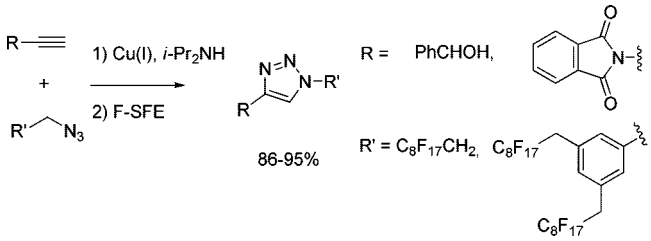
Scheme 107



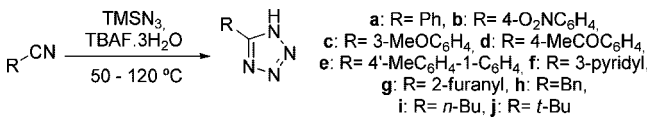
Scheme 108



Scheme 109



Scheme 110



This methodology proved its utility in the successful synthesis of chiral tetrazole analogues of α-amino acids. The conversion of α-aminonitriles to tetrazoles was achieved simply by refluxing the starting material in a mixture of water and 2-propanol at 80 °C with sodium azide in the presence of a catalytic amount of zinc bromide. This expedient route yielded the desired products in yields generally exceeding 90% (Scheme 111).[470] The *N*-protective group proves to be important in the overall yield. In the case where the α-aminonitrile is protected as the benzyl carbamate, the yields are generally over 90%, whereas other protective groups tend to cause some erosion of the final yield, in particular, the *N*-toluenesulfonyl moiety (76% yield).[470]

5. Six-Membered Rings

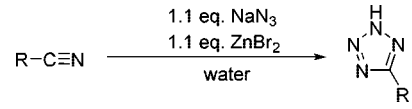
5.1. Containing One Nitrogen Atom

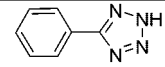
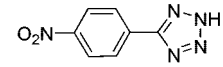
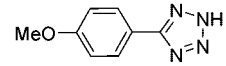
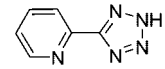
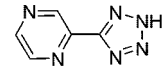
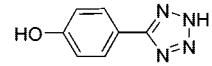
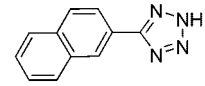
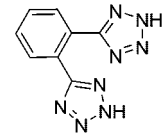
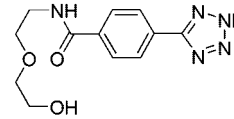
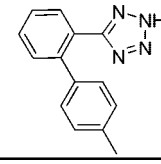
5.1.1. Solvent-Free Reactions

The simplest six-membered N-heterocyclic compound, piperidine, can be modified at the nitrogen position in a solvent-free Mannich reaction by the use of infrared light. The experimental procedure consists of irradiating a mixture of a phenol, formaldehyde, and piperidine with a medicinal infrared lamp (which reaches 120−180 °C) to yield methylpiperidinyl phenols in up to 25 min (Table 55).[471] Morpholine and thiomorpholine can also be used as amines to yield the correspondent phenols after infrared irradiation.

The versatile Diels−Alder reaction can be an efficient method for the preparation of highly substituted pyridines

Table 54



Entry	Temperature (ºC)	*t* (h)	Product	Yield (%)
1	reflux	24		76
2	reflux	24		94
3	reflux	48		86
4	reflux	6		79
5	reflux	2		83
6	140	24		96
7	140	48		73
8	reflux	48		64
9	reflux	12		67
10	170	48		67

under solvent-free conditions. Starting from substituted 1,2,4-triazines through reaction with enamines (generated *in situ*), pyridines can be prepared in high yields under microwave irradiation. Under these conditions, pyrrolidine proved to be a very good choice for the *in situ* preparation of the enamine, regardless of the use of cyclic or acyclic ketones (Table 56). Through the use of cyclic ketones, fused pyridine systems can also be obtained in good yields.[472,473]

One-pot synthesis methodology can be used for the preparation of 2-amino-3-cyanopyridine derivatives. The

Scheme 111

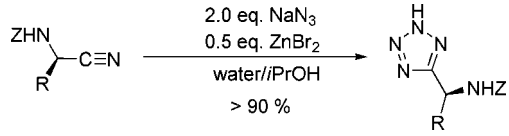
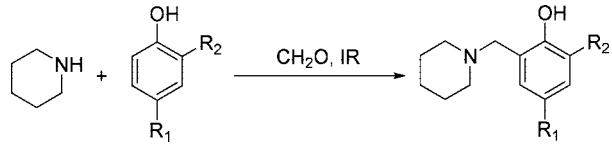


Table 55



entry	R_1	R_2	time (h)	yield (%)
a	*t*-Bu	H	0.4	70
b	H	H	0.3	75
c	*i*-Pr	H	0.3	70
d	H	NO_2	0.35	70

procedure for the synthesis of these compounds in high yields (72−86%) is based on the microwave irradiation of an aromatic aldehyde, methyl ketones, malononitrile, and ammonium acetate for 7−9 min (Scheme 112).[474] Annelated pyridines can be prepared in good yields following a Knoevenagel condensation of β-formyl enamides and cyano derivatives in basic alumina under microwave irradiation,[475] while 2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile can be prepared in 90% yield by triturating a mixture of 2-aminonicotinaldehyde, ethyl cyanoacetate, and piperidine at room temperature (Scheme 113).[476]

The solvent-free methodology has been successfully applied to the preparation of a key intermediate in the synthesis of the antibacterial nalidixic acid. Naphthyridone was prepared through a Jacobs−Gould cyclization reaction at 380 °C in a continuous process in 79% conversion (Scheme 114).[477]

Recently, fused benzopyrazolo[3,4-*b*]quinoline derivatives were prepared through the three-component solvent-free reaction of 5-aminopyrazoles, benzaldehydes, and β-tetralone accomplished by a fusion procedure or through condensation of α-tetralone benzylidene derivatives with aminopyrazoles (Scheme 115). These reactions were performed under conventional heating conditions (120 °C) in short times (1.5−7 min), and the products were obtained in reasonable yields (50−80%).[478]

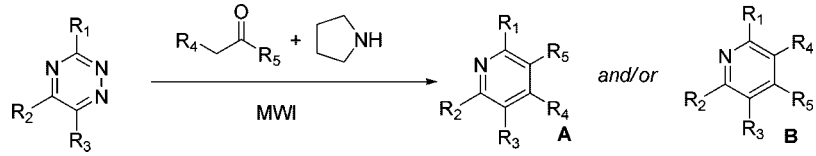
Several methods for the preparation of pyridine derivatives through oxidation of Hantzsch 1,4-dihydropyridines are described (Scheme 116). Under solvent-free conditions, it can be done through the use of bismuth(III) chloride supported in HZSM-5 zeolite under MWI,[479] by phenyliodine(III) bis(trifluoroacetate) at room temperature or with sulfur under MWI (5−7 min),[480] and by microwave-induced hydrogen transfer to carbonyl- or nitro-substituted olefins in presence of silica gel. In this last procedure, it was observed that the presence of a large substituent at the 4-position decreased the reaction yield.[481] Recently, a system composed of $NaNO_2$, wet silica, and methanesulfonic acid was developed for the room temperature, solvent-free aromatization of 1,4-dihydropyridines.[482]

For the preparation of pyrazolo[3,4-*b*]pyridines, it was observed that these compounds could be synthesized by microwave-induced cycloaddition of 2-azadienes with aromatic and aliphatic nitroalkenes[483,484] or by irradiating a mixture of 5-aminopyrazolone, benzoylacetonitrile, and benzaldehydes with microwaves.[485]

For the preparation of 2,4,6-triaryl pyridines (Krönke pyridines), a mixture of 1,3-diaryl-2-propen-1-ones and NH_4OAc in presence of catalytic amount of acetic acid can be heated at 100 °C for 4 h to yield 2,4,6-triaryl in excellent yields (93−98%).[486]

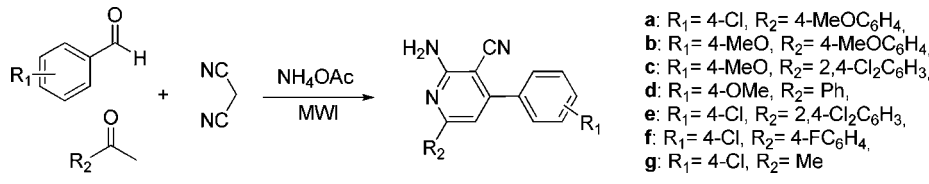
Concerning pyridine substituent modification, solvent-free synthetic methods have also been developed. For instance, bis-thioureas and bis-thiosemicarbazide functional groups can be introduced in a two-step reaction. First, pyridine-2,6-dicarbonyl diisocyanate has to be synthesized, which can be achieved through reaction of pyridine-2,6-dicarbonyl dichloride with ammonium thiocyanate in the presence of PEG-400 (4 mol %) at room temperature. The second step consists of reacting this diisocyanate with an aryl amine or an aryl hydrazine (Scheme 117).[487] Similar to the described methodology for introducing an alkyl chain in the imidazole ring under MWI in order to synthesize ionic liquids, pyridines can also be modified through reaction of pyridine with alkyl

Table 56

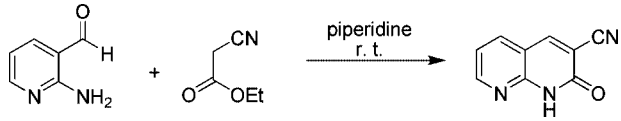


entry	R_1	R_2	R_3	R_4	R_5	time (min)	yield (%)	**A/B**
1	Py	Ph	H	H	Ph	30	71	6:1
2	Py	Ph	H	Me	Et	60	60	2:1
3	Py	Ph	H	*n*-Pr	H	30	81	only **A**
4	Py	Ph	H	Ph	H	15	85	only **A**
5	Py	Fur	Fur	*n*-Pr	H	60	69	only **B**
6	Py	Fur	Fur	Ph	H	15	82	only **B**
7	Py	H	H	*n*-Pr	H	15	67	only **B**

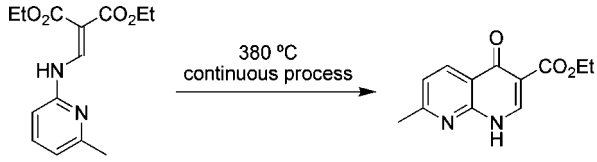
Scheme 112



Scheme 113



Scheme 114



halides to produce pyrazolium ionic liquids,[201] while 4-methyl pyridine quaternary salts can be condensed with aromatic aldehydes in a microwave oven to afford some hemicyanine dyes.[334]

Through the three-component aza-Diels−Alder reaction catalyzed by $Yb(OTf)_3$ at room temperature, 2,5-disubstituted 2,3-dihydro-4-pyridones can be achieved in moderate to high yields. The reaction proved to be efficient using a wide range of aldehydes, including aromatic, aliphatic, heteroaromatic, and olefinic aldehydes (Table 57).[488,489]

Hantzsch 1,4-dihydropyridines can be prepared in good to excellent yields by condensation of ethyl acetoacetate and a range of aldehydes in the presence of an ammonium salt at 80 °C (conventional heating). Ammonium formate and ammonium fluoride proved to be efficient ammonium sources under these reaction conditions,[490,491] while the use of ammonium acetate proved to be very effective when the reaction was performed under microwave irradiation.[492] Furthermore, ammonium acetate can be used in the one-pot synthesis of decahydroacridine derivatives, starting from 2 mol of dimedone with subsequent reaction with an aldehyde.[493] *N*-Hydroxyethyl-1,4-dihydropyridines were recently synthesized through solvent-free condensation of methyl acetatoacetate, an aromatic aldehyde, ethanolamine, and acetic acid as ethanolammonium acetate at 40 °C. While the reaction times were slightly decreased through the use of iodine as catalyst, the reaction yields were improved (85−98%) when 15 mol % of iodine was used.[494]

Pyridinones and dihydropyridinones can be quantitatively obtained by microwave-induced reaction of enaminocarbonyl compounds and 4-ethoxymethylene-2-phenyloxazol-5(4*H*)-ones and 4-arylidene-2-phenyloxazol-5(4*H*)-ones, respectively (Scheme 118). This method seems particularly interesting since it leads to the preparation of compounds structurally related to Hantzsch 1,4-dihydropyridines in quantitative yields without the use of any solvents and no need to perform any work-up procedure.[495]

Pyrimidin-4-ones can be achieved in 15−20 min with good yields (70−75%) under solvent-free conditions by irradiating a mixture of an aminopyrimidine, benzoylacetonitrile, and benzaldehydes with microwaves (Scheme 119).[496] Furthemore, pyrazolo[3,4-*b*]pyridines can be obtained under the same reaction conditions by reaction of 5-aminopyrazolone instead of aminopyridine,[485] and bispyrazolopyridines are formed by reaction with aminopyrazole.[497] On the other hand, a diastereoselective one-pot annulation of pyrimidine ring on azoles can be performed by the irradiation with microwaves of an azole Schiff base, glycine, and acetic anhydride to yield fused-ring pyrimidines,[498] and 1,3,4-oxadiazolopyrimidin-5-ones or the thiadiazolo analogue could be obtained by reaction of 1,3-oxathiolan-5-one and an azole Schiff base.[499]

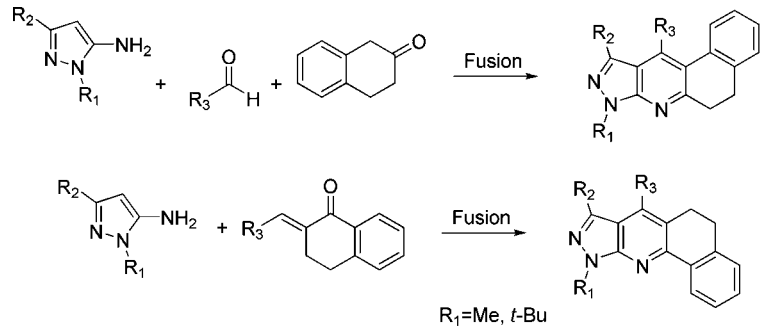
Polysubstituted tetrahydropyridines can be prepared at room temperature using the condensation of aromatic aldehydes and Brassard's dienes in presence of anilines and $BF_3 \cdot Et_2O$ as Lewis acid catalyst (50 mol %). The use of electron-donating group substituted aldehydes seems to improve the reaction yield in this solvent-free reaction (Scheme 120).[500]

The synthesis of 4-oxo-tetrahydropyridines can be achieved by simple reaction of 2-dimethylamino derivatives with primary amines in a microwave oven in the absence of a solid support (Table 58).[501]

The solvent-free, microwave-assisted synthesis of 3,4-dihydropyridones can be performed by one-pot condensation from Meldrum's acid, methyl acetoacetate, and aromatic aldehydes in presence of ammonium acetate (Table 59). Through comparison with the conventional heating procedure, the higher yields and reactivity were attributed to an electrostatic stabilization of the transition state on a microwave environment.[502]

For the introduction of a substituent on the nitrogen atom of substituted pyridones, it was observed that *N*-acetyl pyridones react with acetylenedicarboxilates in presence of alumina under MWI to afford Michael-type N-adducts[503] and 2-pyridone reacts with benzyl halides under MWI or conventional heating being alkylated in the nitrogen atom with the selectivity dependent on the halide or the microwave power used. In this case, it was observed that competitive C-alkylation was favored with soft leaving groups (I > Br > Cl) as can be demonstrated by the rapid and quantitative N-alkylation under MWI or conventional heating when benzyl chloride is used.[504]

Scheme 115



R_1=Me, *t*-Bu
R_2=Ph, 4-ClC_6H_4
R_3=4-FC_6H_4, Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-Pyridyl

Scheme 116

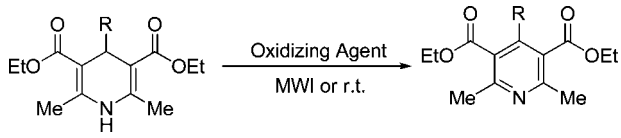
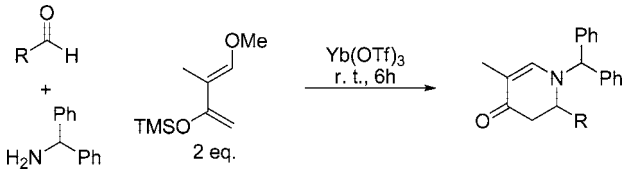


Table 57



entry	R	yield (%)
1	Ph	77
2	2-MeC_6H_4	83
3	3-MeC_6H_4	79
4	4-MeC_6H_4	72
5	2-$MeOC_6H_4$	78
6	3-$MeOC_6H_4$	78
7	4-$MeOC_6H_4$	74
8	2-ClC_6H_4	76
9	3-ClC_6H_4	68
10	4-FC_6H_4	52
11	2-furyl	78
12	2-pyridyl	75
13	PhCH=CH	62
14	C_6H_{11}	86
15	Me_2CH	54
16	*n*-Pr	51

For the preparation of naphthyridin-5-ones derivatives, 1,6-naphthyridines can be cyclized with nitriles in the presence of a catalytic amount of piperidine at room temperature (Table 60). This procedure in the microwave-induced reaction can also be used with the expected main advantage of decrease in the reaction time from hours to minutes accompanied by a yield improvement.[505]

Under solvent-free conditions and by conventional heating, the reaction between 1,2-diaza-1,3-butadienes and 1,2-diamines led to the formation of the correspondent piperazinones in reasonable yields (Table 61). This method proved to be very interesting since the same reaction when performed in acetonitrile or methanol led to the formation of pyrazines.[29] Going back to the microwave-assisted synthesis, 2,5-piperazinediones can be efficiently prepared through the cyclization of *N*-Boc dipeptide esters in few minutes or through conventional heating in several hours. Regardless of the severe reaction conditions (200 °C in conventional heating), there seems to be no racemization of the final products.[506,507] Under microwave irradiation, 1-arylpiperazines can be efficiently synthesized through reaction of substituted anilines and bis(2-chloroethyl)amine hydrochloride.[508]

With a montmorillonite K-10 clay and microwave irradiation, the cyclodehydrazination of salicylaldehyde semicarbazones can be performed in a couple of minutes in order to obtain 1,3-oxazin-2-ones derivatives in very good yields (Table 62).[509]

5.1.2. Reactions in Aqueous Media

The synthesis of a variety of six-membered heterocycles has been accomplished in water using different methodologies. The suitability of water as medium for Diels−Alder reaction has been clearly demonstrated over the last years. In a clear demonstration of this fact, Grieco et al. reported the aza-Diels−Alder reaction in aqueous media. The cyclocondensation of dienes with simple iminium salts generated under Mannich conditions, originated carboxyclic structures either by intermolecular or by intramolecular processes (Scheme 121).[510]

Following Grieco's seminal work on the aza-Diels−Alder, Wang et al. reported the catalyzed version of this reaction using lanthanide(III) trifluromethanosulfonates as catalysts in water. This method extended the scope of this reaction to a variety of aldehydes and dienes and the results obtained are listed in Table 63.[511]

Based on their early findings, Wang et al. applied the developed methodology to the synthesis of azasugars. The aza-Diels−Alder reaction catalyzed by $Nd(OTf)_3$ occurred *in situ* with aldehyde. The overall yield for the three steps was 35% as shown in Scheme 122.[512]

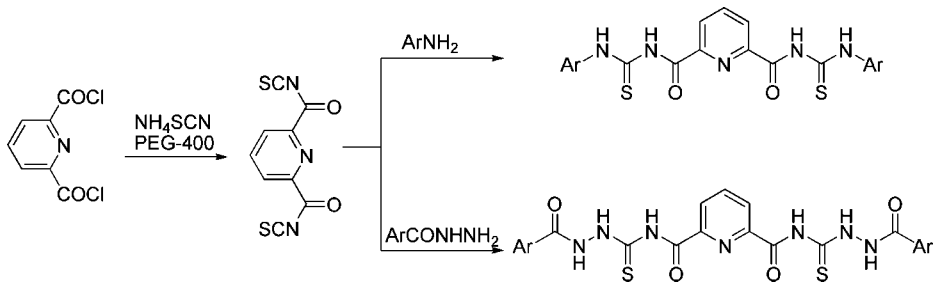
Akiyama et al. explored the aza-Diels−Alder reaction of Danishefsky's diene with aldimine generated *in situ* from aldehydes and amines. This transformation afforded excellent yields of dihydro-4-pyridones under the influence of HBF_4. The best solvent system was identified as methanol/H_2O (Table 64).[513]

Different from the previous case where a Brønsted acid was used to promote the cycloaddition, Kobayashi et al. reported the aza-Diels−Alder reaction catalyzed by silver triflate. The reaction proceeded smoothly on water in the presence of 10% of AgOTf at room temperature (Table 65).[514] This study revealed that the exclusive water medium is more efficient than a THF/water system in which only 63% of product was obtained. This difference was attributed to a slower hydrolysis of the Danishefsky's diene under heterogeneous reaction conditions.[514]

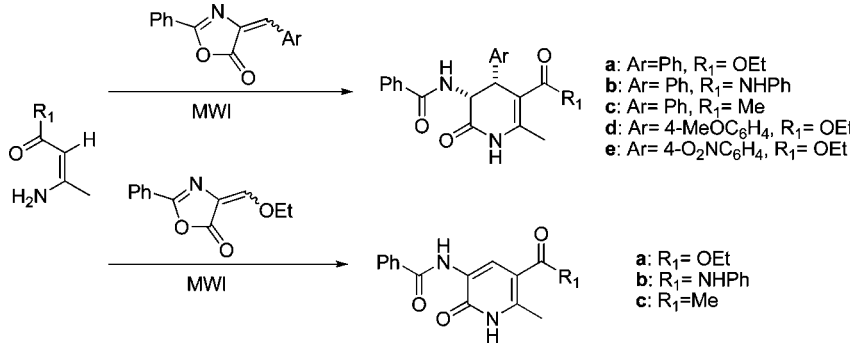
The three-component reaction was evaluated using the same catalytic system in water. The imine was generated *in situ* via the reaction of the amine and the aldehyde catalyzed by AgOTf (10 mol %). To this mixture, the diene was slowly added (45−60 min), and the mixture was allowed to react at room temperature. The results obtained are listed in Table 66.[514]

Pursuing different catalytic systems for this aza-Diels−Alder reaction, Kobayashi et al. found that alkaline salts such as

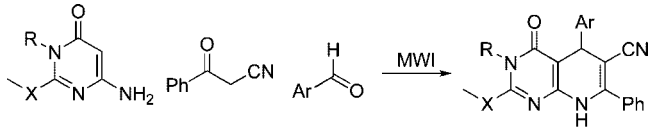
Scheme 117



Scheme 118



Scheme 119



the NaOTf can efficiently promote this cyclization in water, either as a two- or as a three-component reaction (Table 67).[515]

Finally, Akiyama et al. reported the aza-Diels−Alder reaction of Danishefsky's diene with aldimines catalyzed by montmorillonite K-10. A distinguishing feature of this three-component reaction is the fact that aliphatic aldehydes reacted smoothly in the presence of small amounts of montmorillonite K-10 in water, water/acetonitrile, or acetonitrile (Table 68).[516]

Six-membered heterocycles were synthesized following an intramolecular Diels−Alder protocol catalyzed by indium(III) trifluoromethanosulfonate in aqueous media by Taguchi et al. This method takes advantage of the well-known catalytic activity of some rare earth metals ($Sc(OTf)_3$, $Yb(OTf)_3$, or In(III) salts), which act as Lewis acids.[517] The reaction afforded the cycloaddition adduct in 74% yield with a remarkable diastereoselectivity, providing only the *endo* stereoisomer (Scheme 123).

Exploring the versatility of intramolecular Diels−Alder reaction as an adequate method to prepare complex carbocyclic structures, Grieco et al. showed that water is the solvent of choice to perform the intramolecular imino Diels−Alder reaction. As shown in Scheme 124, iminium salt cyclization in water afforded the cyclic tertiary amine in 80% yield, whereas only 13% of the tricyclic compound was obtained when the iminium salt was exposed to a 5.0 M lithium perchlorate in diethyl ether solution.[518]

The presence of water was proven to be determinate for the success achieved by Floreancig et al. on the preparation of piperidines following a cyclization catalyzed by gold catalysts.[519] In this report, homopropargylic ethers containing pendent nitrogen nucleophiles reacted with electrophilic gold catalysts in the presence of water to afford the desired heterocyclic units in moderate to good yields. The authors presented a possible mechanism for oxacycle formation that starts with ketone formation through alkyne

Scheme 120

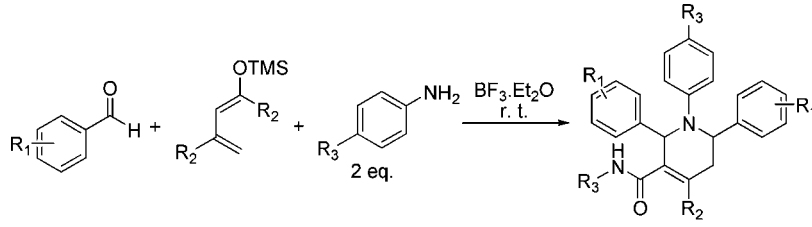
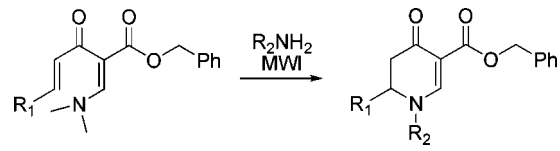


Table 58



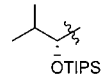
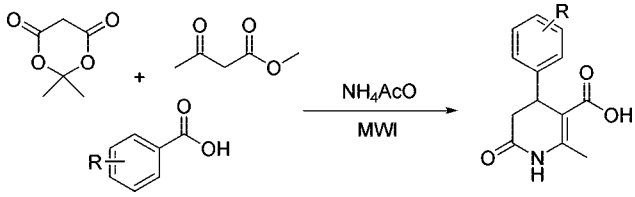
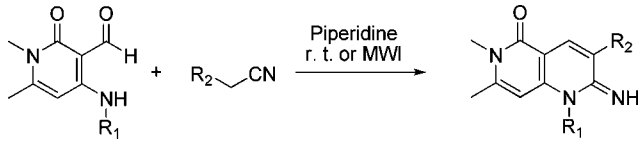
Entry	a	b	c	d	e	f	g
R_1					cyclo-hexyl	Ph	
R_2	$HOCH_2CH_2$-	4-$MeOC_6H_4$	MeO_2CCH_2-	MeO_2CCH_2-	4-$MeOC_6H_4$	4-$MeOC_6H_4$	
Yield (%)	79	60	72	86	54	70	70

Table 59



entry	R	time (min)	yield (%)
1	H	15	86
2	3- NO_2	10	82
3	4- NO_2	15	83
4	2-Cl	10	91
5	4-Cl	10	89
6	4-MeO_2C	15	81
7	2,4-$(NO_2)_2$	10	89

Table 60



			room temperature		microwave irradiation	
entry	R_1	R_2	time (h)	yield (%)	time (min)	yield (%)
1	$PhCH_2$	CO_2Me	48	74	3	77
2	$PhCH_2$	CO_2Et	48	29	3	80
3	$PhCH_2$	CO_2CHMe_2	48	67	3	82
4	$PhCH_2CH_2$	CO_2Me	48	72	3	76
5	$PhCH_2CH_2$	CO_2Et	48	59	3	71
6	$PhCH_2CH_2$	CO_2CHMe_2	48	68	3	79

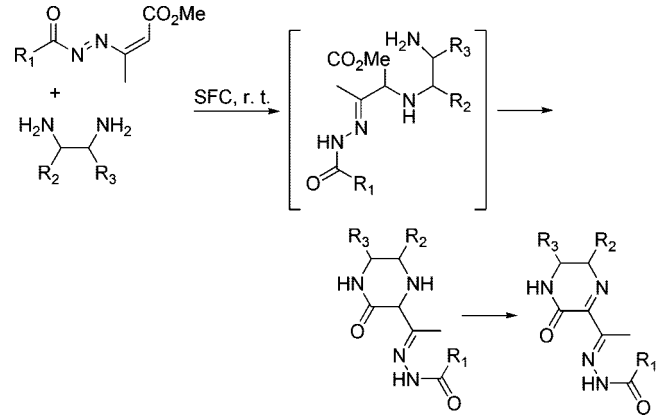
hydration followed by β-elimination of the methoxy group to form the enone. Gold-mediated conjugated addition of the nucleophilic group affords the desired products. Considering the nature of the nitrogen group, sulfonamides and most carbamates reacted smoothly to yield piperidines though *tert*-butyl carbamate did not afford any cyclization most likely due to steric interactions. Free amines and anilines also failed to react, indicating that the nitrogen basicity is determinant for achieving successful cyclizations (Scheme 125).

5.1.3. Reactions in PEG or PEG Tag Approaches

The molecular structure of terpyridine is an important synthon in supramolecular chemistry and is gaining some importance as the basis for future anticancer and antimicrobial agents (Scheme 126). Smith and Raston substituted the conventional solvent-based method by a new protocol based on a polymeric solvent PEG_{300}.[520] With this new protocol, the terpyridines were obtained in high purity in a one-pot procedure during 4 h (overall 50% yield) without the formation of undesired side products.

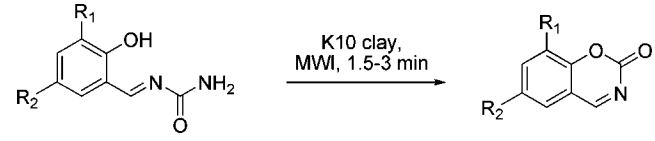
Taddei et al. optimized the synthesis of tetrasubstituted pyridines supported in soluble polymer $MeOPEG_{5000}$ using microwave technology (Scheme 127).[521] A suitable choice of solvent for the reaction allowed all steps to run in good yields and provided an easy method for product separation (by refrigeration and crystallization). Organic solvent was always required since the melted support did not furnish the same level of activity (slower reaction with lower yields).

Table 61



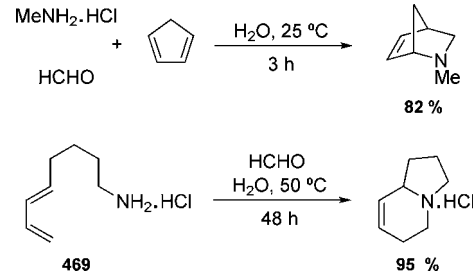
entry	R_1	R_2	R_3	temp (°C)	yield (%)
1	NH_2	H	H	25	70
2	NH_2	-$(CH_2)_4$-		45	42
3	NH_2	Ph	Ph	90	65
4	*t*-BuO	H	H	25	88
5	*t*-BuO	-$(CH_2)_4$-		45	47

Table 62



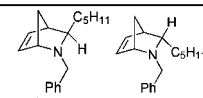
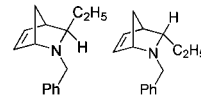
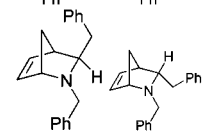
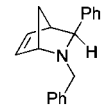
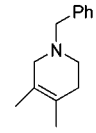
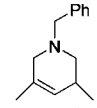
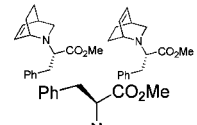
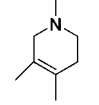
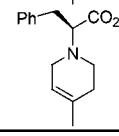
entry	R_1	R_2	yield (%)
1	H	H	84
2	H	Br	86
3	Br	Br	87
4	H	Cl	90
5	Cl	Cl	94
6	F	H	91
7	MeO	H	88
8	H	NO_2	90
9	NO_2	NO_2	93
10	I	I	93

Scheme 121

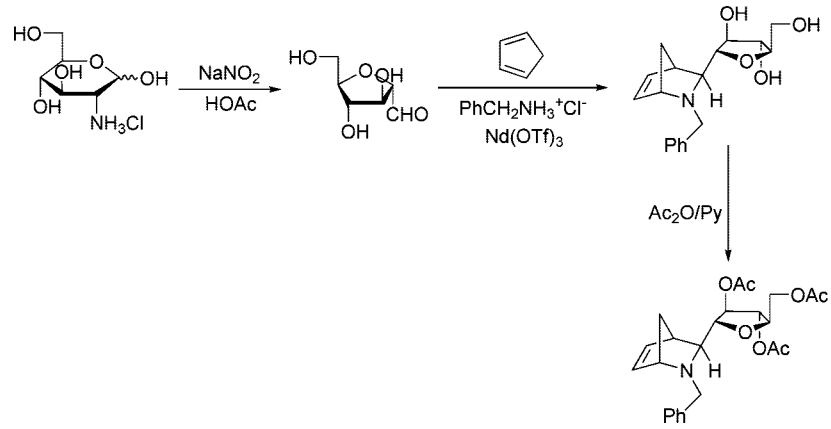


The 2,3-dihydro-4-pyridinones are complex molecular compounds that can be obtained via cycloaddition between imines and Danishefsky's diene. Ding and Guo prepared this type of heterocycle supported on a soluble polymer support, PEG_{3400}. Initially, the amine substrate was chosen to be anchored in the support, and this was achieved by a straightforward methodology. Next, this modified support was reacted in the presence of several aldehydes and Danishefsky's diene to furnish the desired supported heterocycle via a three-component one-pot reaction (Scheme 128). The unsupported heterocycle was isolated after basic hydrolysis, generally in very good yields (up to 99% yields) and high purities (up to 98%).[522]

Table 63

Entry	Starting Materials			Catalyst	Products	Ratio	Yield (%)
	Aldehyde	Diene	Amine	$Ln(OTf)_3$			
1	$CH_3(CH_2)_4CHO$		$BnNH_3^+Cl^-$	$Pr(OTf)_3$		2.9/1	68
2	CH_3CH_2CHO		$BnNH_3^+Cl^-$	$La(OTf)_3$		2.5/1	64
3	$PhCH_2CHO$		$BnNH_3^+Cl^-$	$Yb(OTf)_3$		4/1	72
4	PhCHO		$BnNH_3^+Cl^-$	$Yb(OTf)_3$		-	7
5	$CH_3(CH_2)_4CHO$		$BnNH_3^+Cl^-$	$Ln(OTf)_3$	No products	-	-
6	$CH_3(CH_2)_4CHO$		$BnNH_3^+Cl^-$	$Ln(OTf)_3$	No products	-	-
7	CH_2O		$BnNH_3^+Cl^-$	$Nd(OTf)_3$		-	93
8	CH_2O		$BnNH_3^+Cl^-$	$Yb(OTf)_3$		-	92
9	CH_2O		L-phenylalanine methyl esther	$Nd(OTf)_3$		1/3	84
10	CH_2O		L-phenylalanine methyl esther	$Nd(OTf)_3$		-	98
11	CH_2O		L-phenylalanine methyl esther	$Nd(OTf)_3$		-	96

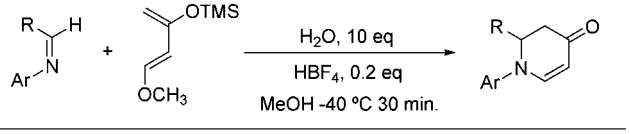
Scheme 122



When the substrate immobilized was the aldehyde, the three-component one-pot reaction afforded lower yields (about 50%). It was necessary to induce imine formation before adding the diene in order to achieve the same level of reactivity observed when amine was immobilized.[523] This result is consistent with a simultaneous work presented by Wang et al.[132]

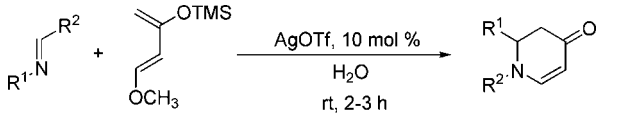
Wipf et al. proved that PEG-supported Burguess reagent is a suitable dehydrating agent for preparation of oxazines and thiazines, generally surpassing in terms of yield the traditional Mitsunobu reaction (Scheme 129).[524] This protocol also gives the advantage of allowing easy removal of a secondary product from the reaction mixture just by precipitation.

Table 64



entry	R	Ar	yield (%)
1	Ph	Ph	98
2	*p*-$NO_2C_6H_4$	Ph	87
3	*p*-$CH_3C_6H_4$	Ph	95
4	PhCH=CH	Ph	89
5	Ph	*p*-$MeOC_6H_4$	90

Table 65



Entry	R^1	R^2	Yield (%)
1	Ph	Ph	83
2	*p*-$CH_3OC_6H_4$	Ph	77
3	*p*-BrC_6H_4	Ph	75
4	*p*-BrC_6H_4	Ph	87
5	*p*-$NO_2C_6H_4$	Ph	69
6	Ph, Me	Ph	63
7	Ph, Me	Ph	92
8	Ph	-	57
9	Ph	*p*-BrC_6H_4	83

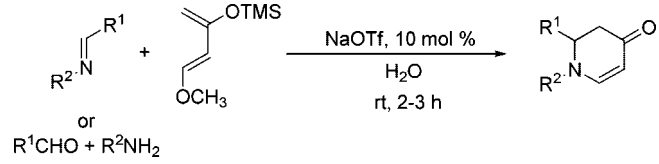
Table 66

entry	R^1	R^2	yield (%)
1	Ph	Ph	63
2	Ph	Ph	80
3	Ph	*p*-BrC_6H_4	90
4	Ph	*p*-$CH_3OC_6H_4$	56
5	*c*-C_6H_{11}	Ph	70
6	*c*-C_6H_{11}	Ph	51
7	$Ph(CH_2)_2$	Ph	53
8	$(CH_3)_2CHCH_2$	Ph	72

5.1.4. Reactions in Ionic Liquids

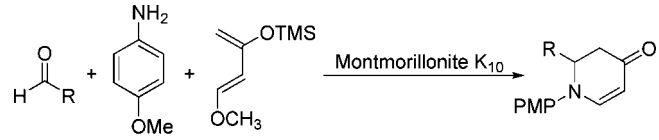
Heteroaryl compounds have important biological properties, and many of their derivatives can be accessed by metal-catalyzed reactions.[525,526] Palladium-catalyzed Heck reactions of the heteroaryl halides, halopyridines, bromothiophenes, and bromoquinoline with the electron-rich olefin vinyl ethers and allyl alcohols were shown to give essentially only the branched olefin in imidazolium-based IL.[527,528] Xiao et al.[529] described the Heck arylation of bromopyridines with the benchmark electron-rich olefin butyl vinyl ether. Following acidic hydrolysis, the resulting branched olefins should readily lead to acetyl pyridines, a class of compounds that are otherwise difficult to access. The arylation of 3-bromopyridine was carried out in [bmim][BF_4] and compared with five normal organic solvents by heating a mixture of the bromide, butyl vinyl ether, and TEA in the presence of $Pd(OAc)_2$ and 1,3-bis(diphenylphosphino)propane (DPPP) (Table 69). With [bmim][BF_4], the vinyl ether was completely arylated to give exclusively the α substituted product (regioselectivity (α/*β*) > 99/1; 100% conversion), while none of the reactions in five organic solvents reported, such as toluene (regioselectivity (α/*β*) = 61/39; 28% of conversion),

Table 67



Entry	R^1	R^2	2-component reaction Yield (%)	3-component reaction Yield (%)
1	Ph	Ph	87	80
2	Ph	Ph	-	80
3	Ph, Me	Ph	72	81
4	Ph	*p*-BrC_6H_4	96	83
5	Ph	*p*-$CH_3OC_6H_4$	83	-
6	*p*-BrC_6H_4	Ph	92	-
7	*p*-$NO_2C_6H_4$	Ph	94	-
8	*p*-$NMe_2C_6H_4$	Ph	87	-
9	Ph	*p*-$CH_3OC_6H_4$	-	74
10	3-py	Ph	-	68
11	*c*-C_6H_{11}	Ph	-	74
12	$Ph(CH_2)_2$	Ph	-	70
13	$(CH_3)_2CHCH_2$	Ph	-	76

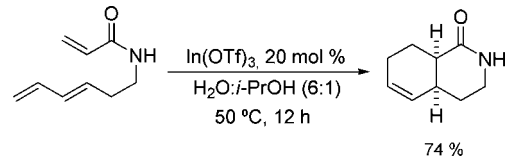
Table 68



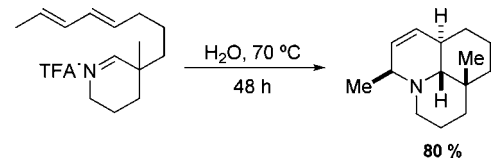
Conditions A: H_2O, 0°C
Conditions B: CH_3CN-H_2O (90:10/v:v), -10°C
Conditions C: CH_3CN, -10°C

entry	R^1	conditions	time (h)	two-component reaction yield (%)
1	*c*-hexyl	A	1.5	85
2	*c*-hexyl	B	1.5	86
3	*c*-hexyl	C	1.5	79
4	$CH_3(CH_2)_2$	A	1.5	85
5	$CH_3(CH_2)_2$	B	1.5	98
6	$CH_3(CH_2)_2$	C	1.5	76
7	$CH_3(CH_2)_2$	B	1.5	91
8	$CH_3(CH_2)_2$	A	1.5	86
9	$CH_3(CH_2)_2$	B	1.5	92
10	$CH_3(CH_2)_2$	C	1.5	61
11	$CH_3(CH_2)_2$	B	1.5	91
12	$BnO(CH_3)CH$	A	2.5	82
13	$(CH_3)_2CHCH_2$	A	4.0	78

Scheme 123

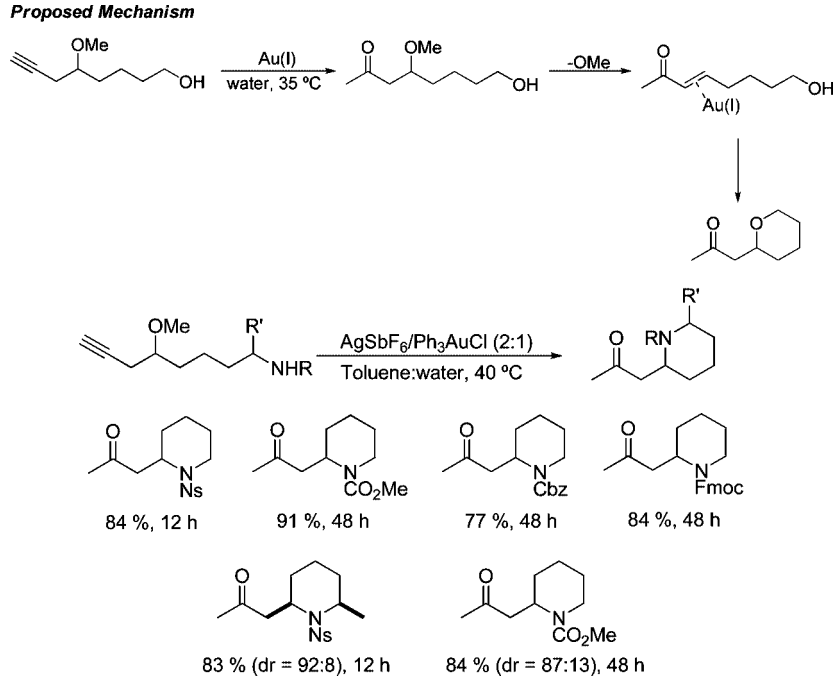


Scheme 124

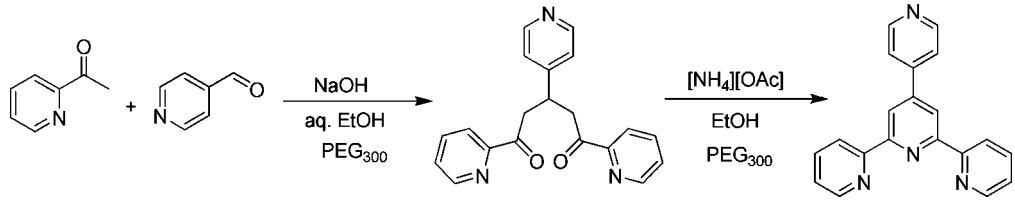


dioxane (65/35; 36%), acetonitrile (62/38; 33%), DMF (71/20; 80%), and DMSO (68/32; 80%), afforded an α/*β* regioselectively near to that observed in IL. The high α regioselective observed suggests that the ionic mechanism

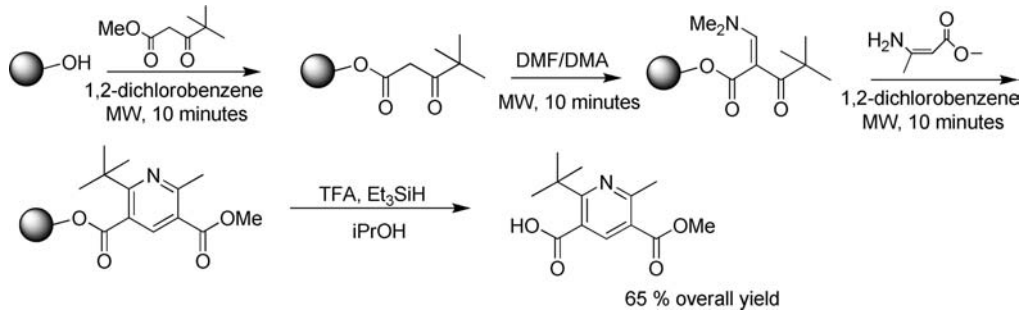
Scheme 125



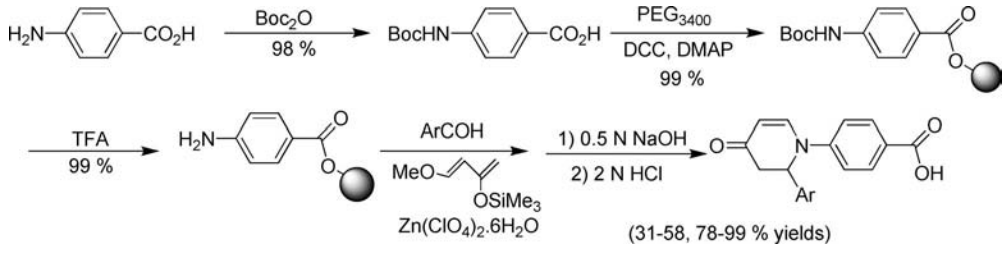
Scheme 126



Scheme 127



Scheme 128



is also important in the arylation by heteroaryl halides in the ionic liquid.[530]

To extend this methodology, some arylation reactions of halopyridines, bromoquinolines and bromothiophenes were performed in IL [bmim][BF_4] (Table 69). All the reactions studied led to exclusive formation of the α arylated olefins,

Scheme 129

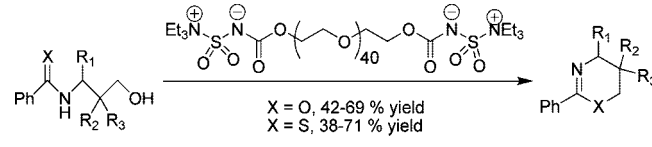
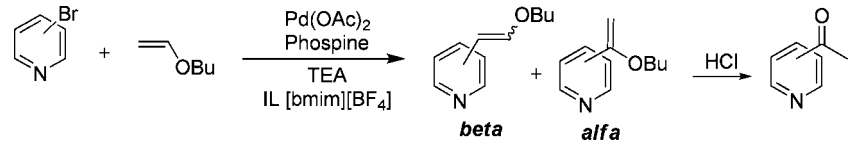
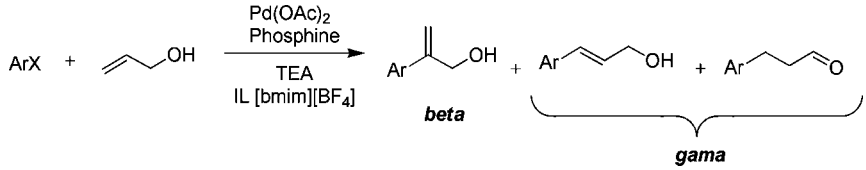


Table 69



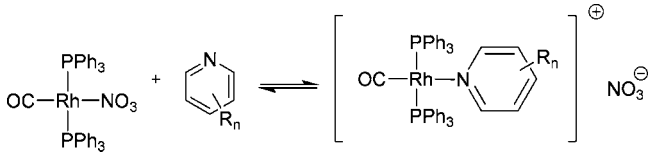
entry	substrate	olefin	product	yield (%)
1	2-bromopyridine	butyl vinyl ether	2-acetylpyridine	88
2	3-bromopyridine	butyl vinyl ether	3-acetylpyridine	81
3	4-bromopyridine	butyl vinyl ether	4-acetylpyridine	75
4	3-chloropyridine	butyl vinyl ether	3-acetylpyridine	69
5	3-bromoquinoline	butyl vinyl ether	3-acetylquinoline	91
6	2-bromothiophene	butyl vinyl ether	2-acetylthiophene	89
7	3-bromothiophene	butyl vinyl ether	3-acetylthiophene	82
8	3-bromopyridine	(2-vinyloxy-ethoxy)-ethene	3-acetylpyridine	77
9	3-bromopyridine	ethyl vinyl ether	3-acetylpyridine	72
10	3-bromopyridine	1-ethyl-hexyl vinyl ether	3-acetylpyridine	71

Table 70



entry	substrate	product	yield (%)
1	2-bromopyridine	2-(pyridin-2-yl)allyl alcohol	86
2	3-bromopyridine	2-(pyridin-3-yl)allyl alcohol	82
3	3-chloropyridine	2-(pyridin-3-yl)allyl alcohol	75
4	3-bromoquinoline	2-(quinolin-3-yl)allyl alcohol	95
5	2-bromothiophene	2-(thiophene-2-yl)allyl alcohol	93
6	3-bromothiophene	2-(thiophene-3-yl)allyl alcohol	89

Scheme 130

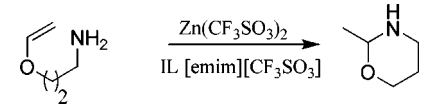


providing the first examples of highly regioselective, intermolecular arylation of electron-rich olefins with heteroaryl halides. The introduction of these functionalities allows the heterocycles to be further synthesized leading to compounds of potentially interesting bioactivities.

In order to explore this highly regioselective Heck arylation methodology, the authors applied it for the preparation of heterocyclic allyl alcohol derivatives by coupling of corresponding allyl alcohols. Generally the arylation of allyl alcohols by aryl halides leads to carbonyl products via isomerization of γ-substituted allyl alcohol (Table 70). Several β-substituted allyl alcohols were prepared by allyl alcohol coupling with halopyridines, bromoquinolines, and bromothiophenes in excellent regioselectivities and yields.

The ILs *N*-hexylpyridinium bistrifylimide ([C_6pyr][Tf_2N]) and [bmim][PF_6] were used to promote the displacement of anionic ligands by pyridine derivatives on *trans*-(Ph_3P)$_2$Rh(CO)NO_3 to a much greater extent than observed in dicloromethane (Scheme 130).[531,532] Ligand substitution is a key step in many homogeneous catalytic processes. ILs have been described as promoting the displacement of anionic ligands by neutral molecules leading to charge-separated species.[533,534] Shaughnessy et al.[535] reported the effect of ILs on the displacement of anionic ligands at a d^8 Rh(I) center by pyridine derivatives, which serves as a model for different catalytic processes. Unlike polar organic solvents, however, weakly coordinating ILs should not compete for coordination to the catalytically active species. The authors mentioned that ILs strongly promote the formation of the charge-separated ligand substitution products and that the extent of this phenomena depends on the nature of the IL selected.[535]

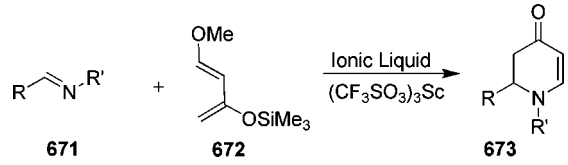
Scheme 131



Muller et al.[536] showed that hydroamination reactions could be efficiently catalyzed in a liquid−liquid two-phase system. For this type of reaction, polar catalyst phase Zn(CF_3SO_3)$_2$ fixed in IL [emim][TfO] and a substrate mixture in heptane was employed successfully (Scheme 131). It is particularly noteworthy that the presence of a highly polar solvent led to a higher intrinsic rate of reaction compared with the corresponding homogeneous catalysis.[537] To test the scope and suitability of two-phase catalysis, three model reactions were explored by Muller and co-workers: (a) the cyclization of 6-aminohex-1-yne first generating the enamine 2-methylpiperidine, which isomerized completely (≥ 99% of conversion) *in situ* to the corresponding imine 2-methyl-1,2-dehydropiperidine under neutral conditions; (b) the reaction between phenylacetylene and aniline originating phenyl-(1-phenylethylidene)-amine; (c) the cyclization of 3-aminopropyl vinyl ether to tetrahydro-2-methyl-1,3-oxazine, which was considerably faster (quantitative conversion achieved within 10 min).

5,6-Dihydro-4-pyridone derivatives have been produced by one-pot aza-Diels−Alder reaction in ionic liquids. The aza-Diels−Alder reaction is well known especially in the

Scheme 132



synthesis of azasugars and their derivatives, which often exhibit unique physical and chemical properties.[538] Normally this reaction is carried out in the presence of Lewis acid catalyst such as $ZnCl_2$, BF_3, and $TiCl_4$ using organic solvents.[539,540] Kitazume and Zulfiqar[541] described this type of reaction by preparing 6-aryl-5,6-dihydro-4-pyridones using microencapsulated scandium trifluoromethanesulfonate as a catalyst in ILs (Scheme 132). For these experiments, the authors prepared new ionic liquids such as 8-ethyl-1,8-diazabicyclo[5.4.0]-7-undecenium trifluoromethanesulfonate and 8-methyl-1,8-diazabicyclo[5.4.0]undecenium trifluoromethanesulfonate from the reaction of 1,8-diazabicyclo[5.4.0]-7-undecene with ethyl or methyl trifluoromethanesulfonate. Initially they studied the aza-Diels−Alder reaction of *N*-diphenyl imine with 1-methoxy-3-(trimethylsilyl)oxybuta-1,3-diene using microencapsulated scandium trifluoromethanesulfonate in ILs 8-ethyl-1,8-diazabicyclo[5.4.0]-7-undecenium trifluoromethanesulfonate ([EtDBU][TfO]) and 1-ethyl-3-methyl-1*H*-imidazolium trifluoromethanesulfonate ([emim][TfO]). The product *N*-phenyl-5,6 dihydro-4-pyridone was obtained at 75% and 67% yield, respectively (Scheme 132).

The authors also developed a second version of a one-pot tandem Mannich−Michael-type reaction where the corresponding imines were initially prepared *in situ* from the reaction of aldehyde and amine in IL, and then 1-methoxy-3-(trimethylsilyl)oxybuta-1,3-diene and microencapsulated scandium trifluoromethanesulfonate (as Lewis acid) were added (Table 71).[541] Successive reuse of the recovered ILs and microencapsulated Lewis acid in the same reaction yielded amounts of product as high as those in the first cycle. After the third cycle, the ILs [EtDBU][TfO] and [emim][TfO] were recovered in more than 90−98% yield compared with the starting IL.

5.1.5. Reactions in Fluorinated Fluids

Shi et al. described the use of the Lewis acid $Sc(OSO_2C_8F_{17})_3$ to perform the aza-Diels−Alder reaction using the Danishefsky's diene in perfluorodecalin/hexane, allowing efficient catalyst recycle and reuse **(**Table 72**)**.[542]

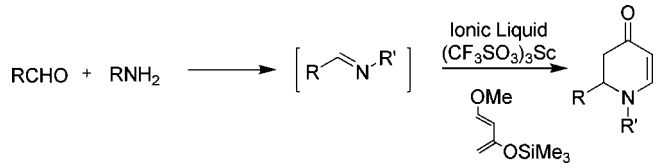
Zhang et al. reported the fluorous tag 4-(1*H*,1*H*,2*H*,2*H*-perfluorodecylsulfonyl)phenol (FluoMar) as the fluorous version of the Marshall resin as an advantage group for amide formation and purification by F-SPE.[543] In Scheme 133, a multistep application of this approach is presented.

5.2. Containing Two Nitrogen Atoms

5.2.1. Solvent-Free Reactions

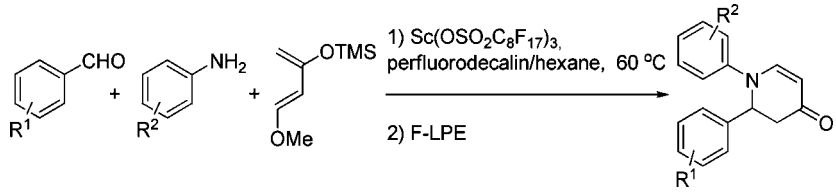
In order to improve the yields obtained in the described classic conditions for the synthesis of 4-aminopyrimidines through trimerization of nitriles, microwave heating has been successfully employed. After the reaction of several nitriles in the presence of a catalytic amount of potassium *tert*-

Table 71



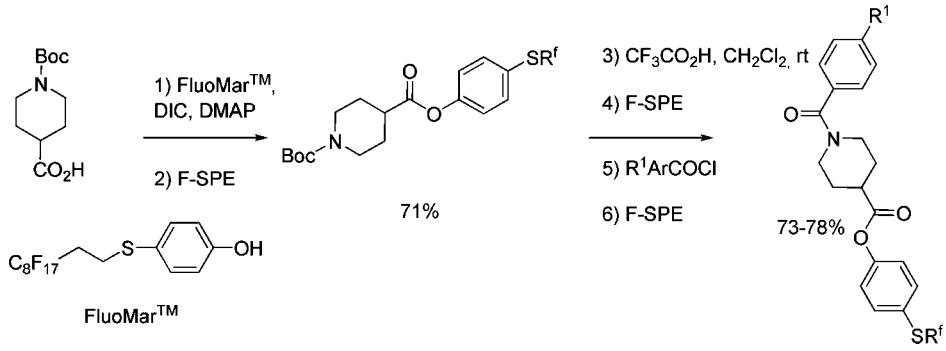
entry	R	R′	ionic liquid	yield (%)	recovered ionic liquid (%)
1	Ph	Ph	[EtDBU][TfO]	82	98
2	Ph	Ph	[emim][TfO]	80	99
3	Ph	3,4-$F_2C_6H_3$	[EtDBU][TfO]	95	92
4	Ph	3,4-$F_2C_6H_3$	[emim][TfO]	99 (1st)	92 (1st)
				99 (2nd)	99 (2nd)
				99 (3rd)	99 (3rd)
5	Ph	4-FC_6H_4	[EtDBU][TfO]	75 (1st)	97 (1st)
				82 (2nd)	95 (2nd)
				95 (3rd)	98 (3rd)
6	Ph	4-FC_6H_4	[emim][TfO]	79	97
7	4-FC_6H_4	Ph	[EtDBU][TfO]	85	98
8	4-FC_6H_4	Ph	[emim][TfO]	95	98
9	4-$CF_3C_6H_4$	Ph	[EtDBU][TfO]	85	98
10	4-$CF_3C_6H_4$	Ph	[emim][TfO]	88	98

Table 72

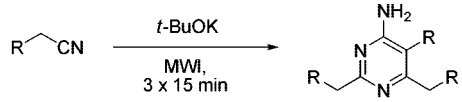


R^1	*p*-Cl	*p*-NO_2	*p*-OMe	H	H	H
R^2	H	H	H	*p*-F	*o*-CF_3	H
yield (%)	73	82	77	84	68	cycles 1−4; 71−74%

Scheme 133



Scheme 134



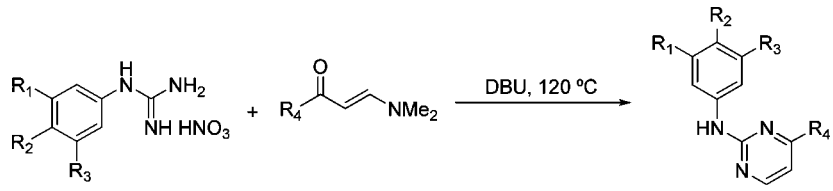
R= 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 2-BrC_6H_4, 3-BrC_6H_4, 4-BrC_6H_4, 2-FC_6H_4, 3-$F_3CC_6H_4$, 4-ClC_6H_4, Ph, -$(CH_2)_3$Ph, Et, Me, H, -$(CH_2)_3$Me, -$(CH_2)_{10}$Me, -$(CH_2)_{16}$Me, 2-thiophenyl, 3-thiophenyl, 3-pyridinyl, 2-pyridinyl, 1-naphtalenyl, 2-naphtalenyl

butoxide, 4-aminopyrimidines can be obtained in good to excellent yields by MWI for 45 min (Scheme 134). Despite the good results that can be obtained with this method, the nitrile should be liquid or have a melting point below 110 °C in order to avoid the formation of a complex mixture of products.[544] Without the use of microwave heating, nitriles can also be trimerized in a similar fashion at 200 °C using milder bases suchas DABCO.[545]

Changing the amino group position in the aminopyridine, 2-substituted ones can be synthesized in moderate to good yields through cyclocondensation of *N*-phenylguanidines and an aryl or aliphatic enaminone in the presence of DBU at 120 °C (conventional heating) for 1 h (Scheme 135).[546] Recently, this procedure was adopted for the microwave conditions; starting from guanidine hydrochloride, urea, or thiourea and using potassium carbonate as base in the absence of any inorganic support, fully aromatized pyrimidines can be obtained in reasonable yields (50−70%) after 10 min irradiation.[547]

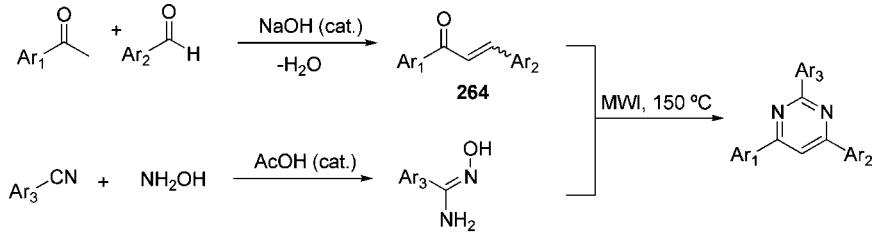
2,4,6-Triarylpyrimidines can be efficiently prepared through a four-component synthesis. This procedure consists of three steps starting from a mixture of a ketone and an aldehyde in the presence of powdered sodium hydroxide at room temperature. After formation of the chalcone, a nitrile, hydroxylamine, and acetic acid are added to the mixture, and after formation of the corresponding amidoxime (2.5 h), the mixture is irradiated with microwaves for 3 min, affording the pyrimidine in good to excellent yields (86−93%) (Scheme 136).[548]

Scheme 135



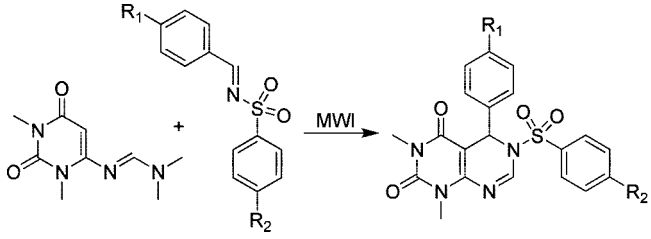
a: R_1= R_2= R_3= MeO, R_4= 4-FC_6H_4
b: R_1= MeO, R_2= R_3= H, R_4= 4-FC_6H_4
c: R_1= R_2= R_3= MeO, R_4= 3-FC_6H_4
d: R_1= R_2= R_3= MeO, R_4= 3-benzyloxyphenyl
e: R_1= R_2= R_3= MeO, R_4= 2-$MeOC_6H_4$
f: R_1= R_2= R_3= MeO, R_4= 2-$O_2NC_6H_4$
g: R_1= R_2= R_3= MeO, R_4= 2,4-$Me_2C_6H_3$
h: R_1= COMe, R_2= R_3= H, R_4= 2-$MeOC_6H_4$
i: R_1= MeO, R_2= R_3= H, R_4= 2-$MeOC_6H_4$
j: R_1= H, R_2= NEt_2, R_3= H, R_4= 2-$MeOC_6H_4$
k: R_1= R_3= H, R_2= F, R_4= 2-$MeOC_6H_4$
l: R_1= F, R_2= R_3= H, R_4= 2-$MeOC_6H_4$
m: R_1= F, R_2= R_3= H, R_4= 1-adamantyl
n: R_1= MeO, R_2= R_3= H, R_4= 1-adamantyl

Scheme 136



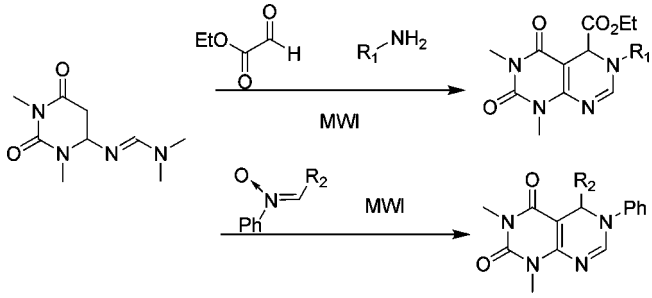
a: Ar_1=Ar_2=Ar_3=Ph
b: Ar_1=Ar_2=Ph, Ar_3=4-BrC_6H_4
c:Ar_1=Ar_2=Ph, Ar_3=4-ClC_6H_4
d:Ar_1=Ar_2=Ph, Ar_3=3-ClC_6H_4
e:Ar_1=Ar_2=Ph, Ar_3=4-$MeOC_6H_4$
f:Ar_1=4-MeC_6H_4, Ar_2=Ar_3=Ph
g:Ar_1=Ar_3=4-MeC_6H_4, Ar_2=Ph
h:Ar_1=4-MeC_6H_4, Ar_2=Ph, Ar_3=4-ClC_6H_4
i:Ar_1=Ph, Ar_2=4-$MeOC_6H_4$, Ar_3=4-ClC_6H_4
j:Ar_1=Ph, Ar_2=Ar_3=4-$MeOC_6H_4$
k:Ar_1=Ar_3=Ph, Ar_2=4-$MeOC_6H_4$
l:Ar_1=Ar_3=Ph, Ar_2=4-ClC_6H_4
m:Ar_1=Ph, Ar_2=4-ClC_6H_4, Ar_3=4-ClC_6H_4
n:Ar_1=Ar_3=Ph, Ar_2=4-$O_2NC_6H_4$
o:Ar_1=Ar_2=Ph, Ar_3=2-naphthyl
p:Ar_1=1-naphthyl, Ar_2=Ar_3=Ph
q:Ar_1=2-naphthyl, Ar_2=Ar_3=Ph

Table 73



entry	R_1	R_2	reaction time (min)	yield (%)
1	Cl	Me	4.5	98
2	H	Me	5	97
3	Me	Me	5	94
4	Me	Cl	5	95
5	NO_2	Me	4.5	90
6	Me	H	4.5	95
7	MeO	Me	5	96
8	EtO	Me	5	95

Table 74

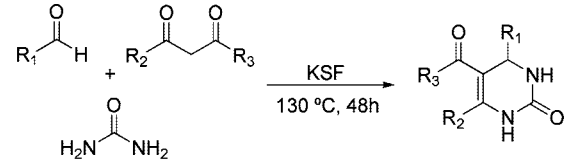


entry	R_1	reaction time (min)	yield (%)
1	Ph	3.5	95
2	4-ClC_6H_4	4.0	85
3	4-MeC_6H_4	3.5	86
4	4-$MeOC_6H_4$	3.0	95
5	4-$NO_2C_6H_4$	4.5	84
6	4-BrC_6H_4	4.0	83
7	Ph	3.5	90
8	4-ClC_6H_4	3.0	88
9	4-MeC_6H_4	3.5	82
10	4-$MeOC_6H_4$	3.0	87
11	4-$NO_2C_6H_4$	3.5	85
12	4-BrC_6H_4	3.5	80

By reaction of a uracil derivative with a *N*-sulfonylimine under MWI, pyrimido[4,5-*d*]pyrimidines can be efficiently obtained in good yields by a [4 + 2] cycloaddition (Table 73). This procedure is also effective in the cycloaddition with coumarin or quinone derivatives.[549] On the other hand, pyrimido[1,2-*a*]pyrimidines can be achieved by reaction of 2-amino-1,4-dihydropyrimidine derivatives with 3-formylchromone or diethyl(ethoxymethylene)malonate (EMME) under microwave irradiation.[550] Similarly, by reaction of EMME with 4-aminothieno[2,3-*d*]pyrimidine derivatives, a three-ring fused system with a thiophene ring can be obtained in good yields (80−83%).[551] Recently, aminopyrazoles were reported to react with 3-(oxo-2-benzofuran-1(3*H*)-ylidene)-pentane-2,4-dione at 150 °C to afford pyrazolo[1,5-*a*]pyrimidines after 1.5−2 min at that temperature.[552]

Pyrimido[4,5-*d*]pyrimidine derivatives can also be prepared starting from uracil derivative 6-[(dimethylamino)-methylene]amino-1,3-dimethyl uracil by reacting it with ethyl glyoxylate and an aryl amine in a microwave oven at 110 °C (Table 74, entries 1−6). The reaction of this uracil derivative with diaryl nitrones under MWI also lead to the formation of pyrimido[4,5-*d*]pyrimidine in good yields (Table 74, entries 7−12).[553] Recently, the preparation of thieno[2,3-*d*]pyrimidines and thieno[3,2-*e*]pyrimidines under microwave irradiation was reported. Through the reaction of *ortho*-amino ester of thiophene derivatives with nitriles in the presence of potassium *tert*-butoxide, these compounds can be prepared in reasonable yields (48−78%) in short reaction times (45−150 s).[554,555]

Scheme 137



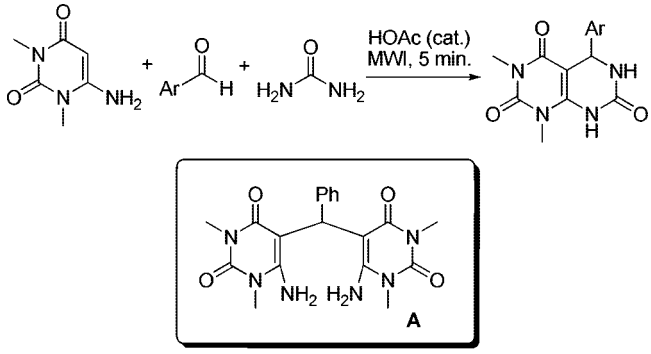
a: R_1= Ph, R_2= Me, R_3= OEt
b: R_1= 4-ClC_6H_4, R_2= Me, R_3= OEt
c: R_1= 4-$MeOC_6H_4$, R_2= Me, R_3= OEt
d: R_1= 4-HOC_6H_4, R_2= Me, R_3= OEt
e: R_1= PhCH=CH, R_2= Me, R_3= OEt
f: R_1= Ph, R_2= Ph, R_3= OEt
g: R_1= Ph, R_2= Me, R_3= Me
h: R_1= Ph, R_2= Me, R_3= Ph
i: R_1= C_4H_9, R_2= Me, R_3= OEt

Biginelli compounds represent a family of heterocycles with great importance as biologically active compounds that could be straightforwardly prepared by condensation of β-dicarbonyl compounds, ureas, or thioureas and aldehydes in presence of strong acids (Biginelli reaction) in a one-pot procedure in ethanol.[556−558] Recently it was disclosed that Lewis acids could considerably reduce the reaction time and at the same time improve the yield compared with the original reaction. This type of compound and its derivatives have shown useful pharmacological and therapeutic properties.[559]

Under solvent-free conditions, this reaction can be efficiently performed between an aldehyde, a β-dicarbonyl compound, and thiourea in presence of Yb(III) catalyst supported on Amberlyst 15 resin at 120 °C for 20 h to afford 3,4-dihydropyrimidine-2(1*H*)-thiones.[560] Similarly, through the use of microwave irradiation, this condensation can be performed using acidic alumina,[492] $FeCl_3$-supported on mesoporous Si-MCM-41[561] or hexahydrate $FeCl_3$,[562] or a catalytic amount of dry acetic acid to absorb and transfer the microwaves to the reaction media.[563] Furthermore, a clay montmorillonite KSF catalyzed Biginelli reaction can also be performed to afford 3,4-dihydropyrimidine-2(1*H*)-ones. This reaction proceeds through condensation of aldehydes, β-keto ester, and urea instead of a thiourea at 130 °C for 48 h (Scheme 137).[564] Recently, diammonium hydrogen phosphate[181] and tungstophosphoric acid ($H_3PW_{12}O_{40}$)[565] were employed as catalysts in the Biginelli solvent-free reaction at 80 °C using urea or thiourea as the nitrogen source. While the former proved to be very efficient for several types of aldehydes (alkyl and aryl), the latter can be immobilized on silica and reutilized; furthermore, several families of dicarbonyl compounds (such as β-ketoamides) can be used without any yield decrease (86−93%). The use of microwaves to induce this condensation, in the absence of an inorganic support, has proven to be somewhat less efficient (30−68% yield) than when conventional heating is used.[566] Ruthenium trichloride was found to be an efficient catalyst for both of these solvent-free reactions. With this catalyst, the reactions can be performed at 100 °C by conventional heating.[567] Interestingly, for all of these procedures, it was observed that worse results were obtained when the reactions were performed in a solvent.

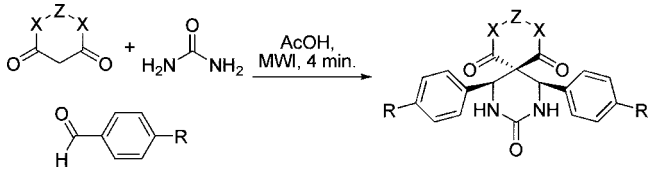
Recently, a series of 2-oxopyrimido[4,5-*b*]- and 2-thio[4,5-*b*]-quinoline derivatives were prepared by reaction of 2-chloro-

Table 75



entry	Ar	yield (%)
1	Ph	87
2	4-MeC_6H_4	86
3	4-$MeOC_6H_4$	75
4	4-ClC_6H_4	80
5	4-FC_6H_4	76
6	4-BrC_6H_4	80

Table 76



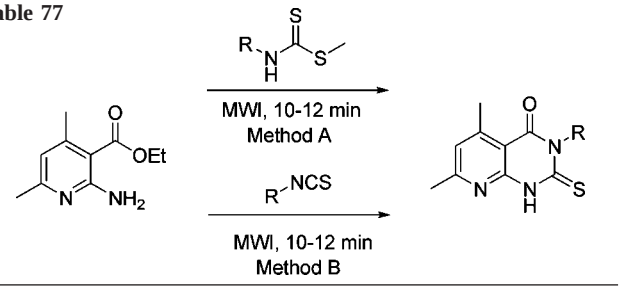
entry	X−Z−X	R	yield (%)
1	O−$C(Me)_2$−O	H	73
2	O−$C(Me)_2$−O	Me	70
3	O−$C(Me)_2$−O	Cl	74
4	O−$C(Me)_2$−O	F	72
5	HN−CO−NH	H	83
6	HN−CO−NH	Me	81
7	HN−CO−NH	Cl	82
8	HN−CO−NH	F	79
9	MeN−CO−NMe	H	82
10	MeN−CO−NMe	Me	80
11	MeN−CO−NMe	Cl	81
12	MeN−CO−NMe	F	83

3-formylquinoline with urea or thiourea, respectively, in the presence of *p*-toluenesulfonic acid under microwave irradiation. The desired products were obtained in good to excellent yields (68−98%) in up to 12 min.[376] Through the condensation of 6-amino-1,3-dimethyluracil, aryl aldehydes, and urea in the presence of a catalytic amount of acetic acid, 5,6-dihydro-1,3-dimethyl-5-arylpyrimido[4,5-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)trione derivatives can be obtained in good yields after microwave irradiation of the reaction mixture for 5 min. The aldehyde uracil condensation product **A** was isolated and identified as the reaction intermediate, which after reaction with urea led to the formation of pyrimido derivatives (Table 75).[568]

spiro-Tetrahydropyrimidinone derivatives can be obtained in good yields through microwave irradiation of a mixture of Meldrum's acid or barbituric acid derivatives, urea, and an aldehyde in presence of a protic acid catalyst, of which acetic acid seems to be the best catalyst (Table 76).[569] Recently, the same reaction was seen to be efficiently catalyzed by a solid heteropolyacid ($H_3PW_{12}O_{40}$) under conventional heating conditions (80 °C, 1 h).[565]

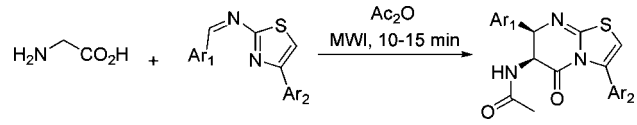
2-Thioxo-4-oxo-tetrahydropyridine derivatives can be efficiently prepared under solvent-free conditions through conventional heating or under microwave irradiation in

Table 77



entry	R	method A yield (%)	method B yield (%)
1	Ph	81	80
2	4-MeC_6H_4	75	76
3	3-MeC_6H_4	75	72
4	2-MeC_6H_4	77	75
5	4-$OMeC_6H_4$	75	72
6	2-$OMeC_6H_4$	77	74
7	4-ClC_6H_4	82	80
8	C_6H_{11}		75
9	*n*-Bu		70

Table 78



entry	Ar_1	Ar_2	yield (%)
1	Ph	Ph	85
2	Ph	4-$MeOC_6H_4$	88
3	Ph	4-ClC_6H_4	90
4	4-MeC_6H_4	Ph	81
5	4-MeC_6H_4	4-$MeOC_6H_4$	85
6	4-MeC_6H_4	4-ClC_6H_4	88

improved yields (Table 77). These compounds can be prepared through the condensation reaction of 2-amino-3-carboethoxy-4,6-dimethylpyridine with methyl-*N*-aryldithiocarabamates or with aryl isothiocyanates.[570]

The annulation of a pyrimidine ring on thiazoles for the production of thiazolopyrimidines can be efficiently achieved in a few minutes through the microwave irradiation of a mixture of glycine, acetic anhydride, and a thiazole Schiff base (Table 78).[571]

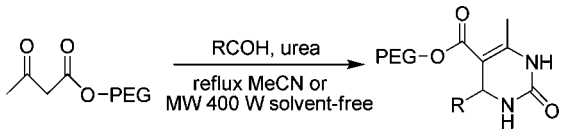
Pyrazolo[3,4-*d*]thiopyrimidines can be efficiently obtained in reasonable yields (53−87%) by reaction of pyrazoles with arylisothiocyanate and thiourea under microwave irradiation.[572] N-Arylation of pyrimidine-2,4-diones can be achieved in reasonable yields (40−87%) through the solvent-free nucleophilic aromatic substitution of aryl halides in presence of Cs_2CO_3, silica, and TBAB at 150 °C. This procedure was also applied to purine nucleobases without yield decrease.[573]

5.2.2. Reactions in PEG or PEG Tag Approaches

Wang and Xia demonstrated that Biginelli heterocycles can be prepared supported in PEG with improved yields and easy purification, in the absence of Lewis acids (Table 79). The fact that no Lewis acid was required is crucial since generally they are not totally compatible with PEG polymers. Under solvent-free conditions and in a microwave oven, the reaction time was reduced without a great decrease of isolated yields.[574]

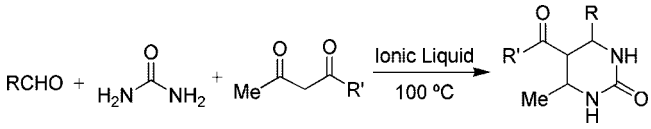
During the microwave irradiation the polymer became liquid facilitating an easier diffusion of the reactants. The heterocycle could be efficiently removed from the support via methanolysis.

Table 79



entry	RCOH	yield (%) PEG support	yield (%) classic conditions	purity (%)
1	Ph	91	42	99.4
2	*p*-OHC_6H_4	82	67	99.8
3	*m*-$NO_2C_6H_4$	94	51	99.5
4	PhCH=CH	89		98.1
5	(2-furyl)	72	36	91.6

Scheme 138



5.2.3. Reactions in Ionic Liquids

3,4-Dihydropyrimidin-2(1*H*)-ones were synthesized in high yields by one-pot three-component Biginelli condensation in the presence of ILs such as [bmim][PF_6] and [bmim][BF_4] as catalysts under solvent-free and neutral conditions (Scheme 138).[575,576] With ILs [bmim][Cl] and [TBA][Cl], low and negligible yields of the products were obtained, respectively.

The novel methodology described using ILs as catalyst showed some considerable advantages, such as shorter reaction times, higher yields, relatively simple catalyst system, free of organic solvent, and easier synthetic procedure. In the case of using ILs, it have been shown that both cation and anion in the ILs played an important role as the catalyst toward the Biginelli condensation.[577−580]

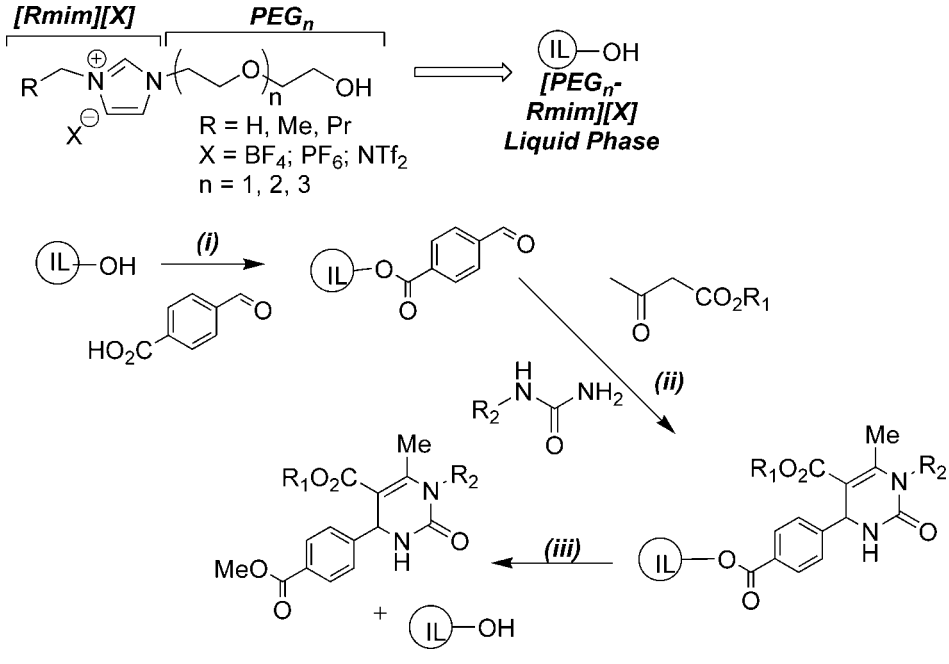
More recently, Bazureau et al.[581] reported a microwave dielectric heating assisted liquid-phase synthesis of Hantzsch 1,4-dihydropyridines[582,583] and Biginelli 3,4-dihydropyrimidin-2(1*H*)-ones, pyridines, and polyhydroquinolines[584] using task-specific ILs as robust and soluble supports. The main advantages of performing reactions under microwave irradiation (MW) conditions are the higher product yields and the significant rate enhancements.[585] From this perspective, MW technology has been applied to rapid synthesis of potential biological molecules useful for combinatorial and medicinal chemistry.[586,587] The authors prepared task-specific ILs on which poly(ethylene glycol) units are grafted and then showed that these new PEG−ILs can be used as alternatives to classical soluble polymeric matrices in combinatorial chemistry (Scheme 139).[588,589]

The use of PEG−IL phases presented several benefits such as compatibility to standard analytical methods, simple product isolation by extraction and washing, the possibility of homogeneous reaction conditions, and the high absorption of MW energy by which the reaction rate is accelerated significantly.

Srinivasan et al.[590] reported a method to prepare 3,4-dihydropyrimidin-2-(1*H*)-ones in good yields, using short reaction time at room temperature and in the absence of any additional catalyst, by the reaction of several aromatic and aliphatic aldehydes with ethyl acetoacetate and urea (or thiourea) dissolved in ILs under ultrasound irradiation (Scheme 140). Like MW technology, the use of ultrasound in organic transformation is known to enhance the reaction rates and yield/selectivity of reactions and in some cases facilitates organic transformations.[591] The one-pot multicomponent reaction promoted by the synergy of combined use of IL as solvent and ultrasound as energy source offers an easy protocol to prepare desired dihydropyrimidinones in excellent yields (83−98%) (Table 80).

This process could be used for aromatic aldehydes containing electron-donating and electron-withdrawing substituents, as well as heterocyclic and aliphatic aldehydes. Several ILs based on 1,3-di-*n*-butylimidazolium [bbim] and 1-*n*-butylimidazolium [bim] series were tested for the typical sonochemical multicomponent reaction of benzaldehyde, ethyl acetoacetate, and urea to produce 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2-(1*H*)-one. The products can be easily isolated by simple dilution and filtration

Scheme 139



Scheme 140

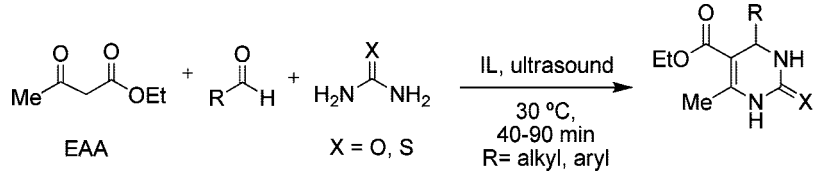
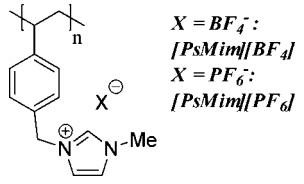


Table 80

entry	ionic liquid	R	atom X	time (min)	yield (%)
1	[bbim][Br]	Ph	O	80	92
2	[bbim][Cl]	Ph	O	75	88
3	[bbim][ClO_4]	Ph	O	95	87
4	[bbim][BF_4]	Ph	O	110	86
5	[bbim][PF_6]	Ph	O	125	83
6	[bim][Br]	Ph	O	60	66
7	[bim][Cl]	Ph	O	60	64
8	[bim][ClO_4]	Ph	O	90	75
9	[bim][BF_4]	Ph	O	45	97
10	[bim][BF_4]	4-$NO_2C_6H_4$	O	70	98
11	[bim][BF_4]	4-$CH_3C_6H_4$	O	45	95
12	[bim][BF_4]	2-FC_6H_4	O	60	90
13	[bim][BF_4]	2-ClC_6H_4	O	30	98
14	[bim][BF_4]	2-BrC_6H_4	O	60	90
15	[bim][BF_4]	3-OMe-4-OH-C_6H_3	O	45	95
16	[bim][BF_4]	C_6H_5−CH=CH	O	50	95
17	[bim][BF_4]	2-pyridyl	O	55	83
18	[bim][BF_4]	2-furyl	O	30	93
19	[bim][BF_4]	*c*-C_6H_{11}	O	50	93
20	[bim][BF_4]	*n*-C_9H_{19}	O	55	87
21	[bim][BF_4]	Ph	S	50	93
22	[bim][BF_4]	4-$OMeC_6H_5$	S	55	97
23	[bim][BF_4]	3,4,5-trimethoxy-C_6H_2	S	70	92

Scheme 141

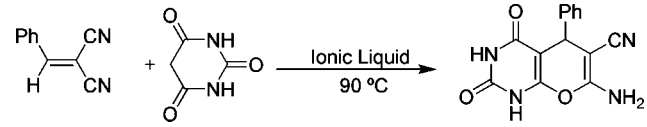


of the precipitated product leaving behind an aqueous filtrate from which the IL can be completely recovered and recycled. Additionally, the authors observed that the reactions did not proceed even after several hours of sonification in molecular solvents such as THF, dichloromethane, ethanol, or acetonitrile instead of the IL under otherwise similar reaction conditions.[590]

Wang et al.[592] described another approach by immobilization of the catalyst on Merrifield resin to obtain polystyrene−methylimidazolium [PsMim]-based re-usable ILs (Scheme 141).[593,594] This new polymer-supported IL as catalyst has been described as a simple, recoverable, and effective method for the Biginelli reaction performed with aromatic aldehydes giving the corresponding pyrimidine-5-carboxylates in high yields (up to 99%) and short reaction times.

Both polymer-supported catalysts, [PsMim][BF_4] and [PsMim][PF_6], catalyze the reaction. However [PsMim][BF_4] produced more insoluble byproducts in ethanol and chloroform compared with [PsMim][PF_6]. The solvent (and temperature) affected the yield; glacial AcOH allowed better isolated yields of product than acetonitrile or ethanol (98% vs 85% or 71%, respectively). The polymer-supported IL [PsMim][PF_6] could be reused at least five times without loss of activity. Several aromatic and aliphatic aldehydes

Table 81



entry	solvent	time (h)	temp (°C)	yield (%)
1	[bmim][BF_4]	3	90	84
2	[emim][BF_4]	3	90	72
3	[bpy][BF_4]	3	90	65
4	toluene	10	90	0
5	$ClCH_2CH_2Cl$	10	90	0
6	[bmim][BF_4]	1	90	57
7	[bmim][BF_4]	3	60	46

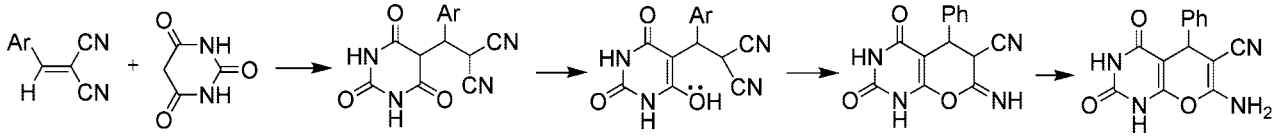
were reacted under optimized conditions in the presence of [PsMim][PF_6] in AcOH at 100 °C for 2 h. Aromatic aldehydes with electron-donating groups R, such as Ph or 4-MeC_6H_4, are appealing for the Biginelli condensation under these experimental conditions (≥ 98% yield), while aromatic aldehydes with electron-withdrawing substituents, such as 2−Cl-C_6H_4, 4−Cl-C_6H_4, 2,4-Cl_2−C_6H_4, 4-NO_2−C_6H_4, or 2-MeO-C_6H_4, gave rise to somewhat lower but still good yields (74−91%). The aliphatic aldehydes (e.g., butanal) were not suited for this type of transformation under the conditions selected.

Pyrano[2,3-*d*]pyrimidine derivatives were prepared in high yields by a condensation reaction between arylmethylidenemalononitrile and barbituric acid using the ILs [bmim][PF_6] and [bmim][BF_4] as solvent under neutral conditions.[595] These compounds are annelated uracils that have shown a relevant biological and pharmaceutical activity such as antitumor, cardiotonic, antihypertensive, and antifungal activities.[596,597]

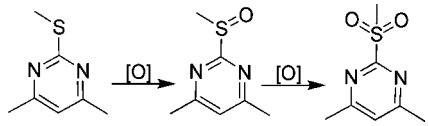
Yu and Wang[595] described the preparation of pyrano[2,3-*d*]pyrimidine derivatives by the condensation reaction between arylmethylidenemalonitrile and barbituric acid in good yields (72−84%) using ILs [bmim][BF_4] and [emim][BF_4] (Table 81). Using the IL 1-butylpyridinium tetrafluoroborate, [bpy][BF_4], the reaction also works well but with lower yield of product (65%). In contrast, no reaction was observed at 90 °C using organic solvents such as toluene and 1,2-dichloroethane. The IL [bmim][BF_4] can be recovered efficiently and reused at least three times, although with a slight loss of activity. This methodology offers significant improvement especially in terms of yields and simplicity of operation. Then, the authors extended this methodology to promote the condensation reaction of several aromatic aldehydes with barbituric acid in IL [bmim][BF_4].

According to the structures of the products, the authors have proposed a possible mechanism for the synthesis of pyrano[2,3-*d*]pyrimidine derivatives involving (a) Michael addition of arylmethylidenemalononitrile to barbituric acid, (b) the resulting product readily undergoing an interconvertible isomerization to form an enol species, and (c) an intramolecular cycloaddition between hydroxyl group and CN to afford an imine, (d) which could be isomerized to give the final product (Scheme 142).

Scheme 142



Scheme 143



Heterogeneous catalytic oxidation of pyrimidine was performed in ILs by using MCM-41 and UVM-type mesoporous catalysts containing Ti or Ti/Ge. Titanium/silica-based mesoporous catalysts are effective systems for selective sulfoxidation of aromatic/aliphatic thioethers, such as 2-thiomethyl-4,6-dimethylpyrimidine, 2-thiobenzylpyrimidine, 2-thiomethylpyrimidine, and 2-thiobenzyl-4,6-dimethylpyrimidine.[598,599] The oxidations were carried out by using anhydrous hydrogen peroxide or the urea−hydrogen peroxide adduct and showed that ILs are very effective solvents, giving higher rates and better sulfoxide selectivity compared with dioxane (Scheme 143). The addition of Ge to Ti was found to increase the rate of oxidation but reduce the selectivity toward the sulfoxide. The sulfoxidation of 2-thiobenzylpyrimidine proceeded with high selectivity (higher than 85%) toward the desired sulfoxide product for all the ILs studied using GeTiSi15 as catalyst and hydrogen peroxide dissolved in dioxane (HPD) as oxidant, while lower selectivities and reaction rates were observed using dioxane as unique solvent (Table 82).[599]

The IL selected showed strong influence on the rate of reaction, particularly for both $[BF_4]$-and $[NTf_2]$-based ILs, in which the rate was found to decrease with increasing chain length and cation size. This cation effect may be related to the viscosity of the IL (most viscous ILs exhibiting the lowest rates) or may reflect how the increasing cation size limits access to the active sites within the catalyst's pores (mesoporous material). In terms of anion effect, it is necessary not only to consider the viscosity or anion size but also the possible interaction of the IL with the catalyst's active sites. For example, in the case of [bmim] cation, the rate was found to follow the order $[TFA]^- > [BF_4]^- \approx [PF_6]- \approx [NTf_2]^- > [TfO]^- > [MsO]^- \approx [Lac]^-$ (where TFA = trifluoroacetate; TfO = trifluoromethanesulfonate; MsO = mesylate; Lac = lactate).

Recently, Hardacre et al.[600,601] described the oxidation of thioethers by two different approaches in order to study the sulfoxidation of 2-thiomethyl-4,6-dimethylpyrimidine using for one case highly dispersed tantalum in a mesoporous-like matrix in ILs containing $[NTf_2]$ as anion[601] and for another case Ti-SBA-15 and UL-TS-1 catalysts in ILs, particularly $[emim][BF_4]$, $[emim][NTf_2]$, and [emim][TfO], allowing high rates, selectivity at high conversion, and good recyclability of the IL/catalyst system.[600]

A comparison with typical organic solvents indicated that much higher activities were possible in the IL, which may be due to activation of the catalyst via a hydrogen bonding interaction. The IL $[emim][BF_4]$ seems to be the best solvent for this type of study. Almost no leaching of titanium was found with Ti-SBA-15 in ILs, whereas significant leaching

Table 82

entry	solvent	selectivity to SO at 30 min (%)	conversion at 30 min (%)	selectivity to SO at 120 min (%)	conversion at 120 min (%)
1	$[emim][BF_4]$	100	26	95	77
2	$[bmim][BF_4]$	100	22	96	73
3	$[C_8mim][BF_4]$	100	7	100	27
4	$[C_6py][BF_4]$	100	10	100	41
5	$[C_8py][BF_4]$	100	11	99	44
6	$[bmim][PF_6]$	100	24	94	75
7	$[bmim][NTf_2]$	100	23	97	70
8	$[bpy][NTf_2]$	100	15	96	57
9	$[bdmim][NTf_2]$	100	15	96	61
10	$[aliquat][NTf_2]$	100	3	95	10
11	$[bmpyr][NTf_2]$	100	2	100	9
12	$[emim][EtOSO_3]$	100	7	100	25
13	[bmim][MsO]	100	3	100	9
14	[bmim][TfO]	100	12	98	49
15	[bmim][TfO]	100	14	96	53
16	[bmim][TFA]	100	41	91	86
17	[bmim][Lac]	100	2	100	8
18	dioxane	95	19	80	41

Scheme 144

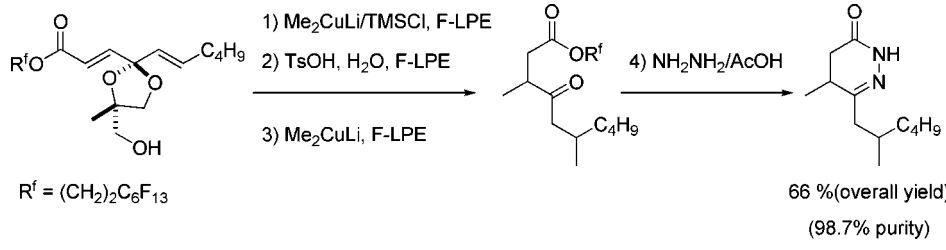
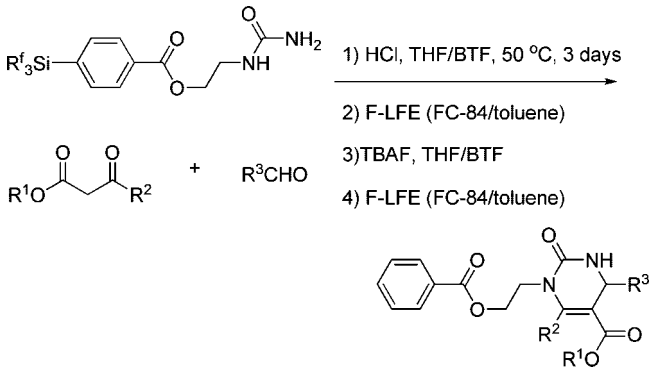


Table 83



entry	R^1	R^2	R^3	yield (%)
1	Et	Me	Ph	71
2	Et	Me	2-naphtyl	55
3	Et	Me	*p*-$MeOC_6H_4$	69
4	Me	Me	2-naphtyl	70
5	Et	Et	2-naphtyl	60
6	Et	Et	Ph	47

was observed for UL-TS-1 catalysts in ILs and organic solvents. The small degree of leaching detected and good recyclability (for five cycles) for Ti-SBA-15 catalysts suggested that in ILs the activity observed is due to a surface-catalyzed process.

5.2.4. Reactions in Fluorinated Fluids

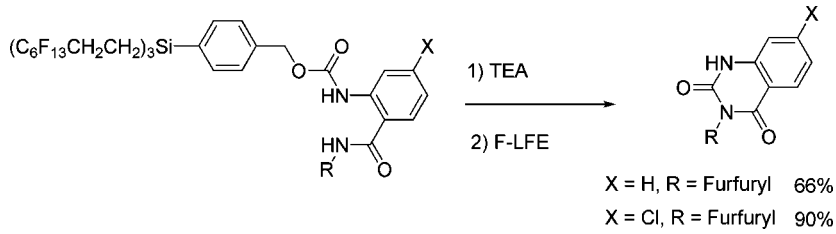
Wipf et al. described the use of 1*H*,1*H*,2*H*,2*H*-perfluorooctanol as an efficient fluorous tag for the preparation of dihydropyridazinone in a multistep synthesis by taking advantage of the fluorous tag for product separation in each step by F-LPE using FC-72 as the fluorinated solvent. In the last cyclization step, the fluorous alcohol tag was removed (Scheme 144).[602]

Curran et al. developed a protocol for the synthesis of dihydropyrimidines by the multicomponent Biginelli reaction based on the use of fluorinated silicon as tag and separation using F-LPE with the toluene/FC-84 solvent system. The fluorous tag was removed from the target product in >90% purity using TBAF and product purification just by using toluene/FC-84 for extraction (Table 83).[603]

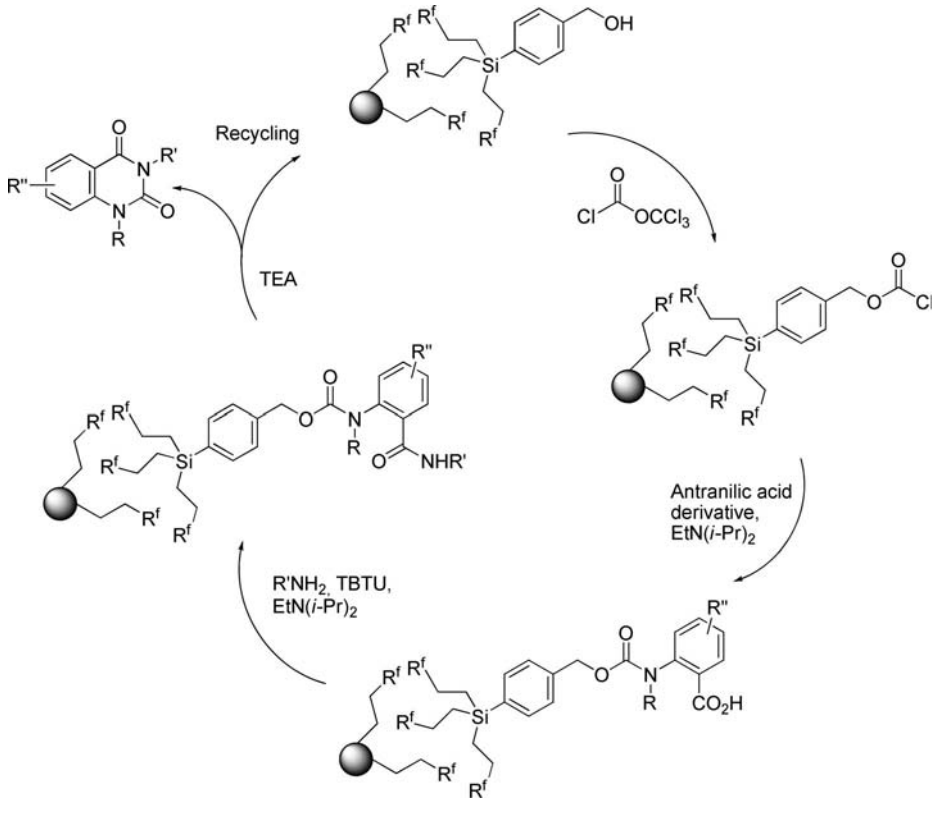
The use of protecting groups containing fluorous tags has been developed for different applications in order to facilitate product purification mainly by taking advantage of purification using the F-SPE approach. Bannwarth et al. used the perfluoro-tagged benzyloxycarbonyl protecting group for the synthesis of quinazoline-2,4-diones in which the alcohol fluorous tag was removed and recycled by extraction with FC-72 (Scheme 145).[604]

Later Bannwarth et al. reported a comparative study for the synthesis of quinazoline-2,4-diones between separation

Scheme 145



Scheme 146



Scheme 147

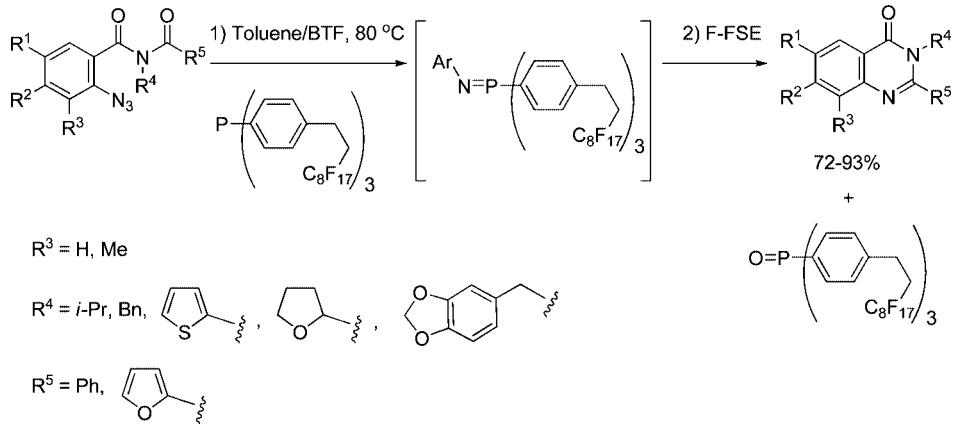


Table 84

entry	R^1	R^2	base (equiv)	yield (%)
1	H	H	DBU (0.1)	91
2	H	H	TEA (0.1)	70
3	MeO	MeO	DBU (0.2)	97
4	H	Cl	DBU (0.2)	96
5	H	Cl	TEA (0.2)	86
6	Cl	H	DBU (0.1)	64
7	Cl	H	DBU (0.2)	67
8	H	NO_2	DBU (0.1)	0
9	H	NO_2	DBU (0.5)	ca. 20

by F-LPE and separation by F-SPE using the previously reported perfluoro-tagged benzyloxycarbonyl protecting group (see Scheme 145). In the case of the F-SPE approach, the authors immobilized the flourous-tag alcohol on a fluorous reversed-phase column in which the quinazoline-2,4-precursors were prepared in a three step synthesis. In the last step, the products were isolated and the fluorous tag immobilized in the solid support was recovered, ready for reuse (Scheme 146).[605] None of the methods provided the best yields for all substrates reported by the authors.

Bannwarth et al. used perfluoroalkyltriphenylphosphine as a fluorous tag for the synthesis of ten 3*H*-quinazolin-4-ones via an aza-Wittig reaction in which the desired product was isolated from unreacted iminophosphorane and perfluorotriphenylphosphine oxide by F-SPE (fluorous reversed silica gel; eluent = acetonitrile). The resulting fluorous phosphine oxide can be recycled to the initial phosphine by reduction with Cl_3SiH (Scheme 147).[606]

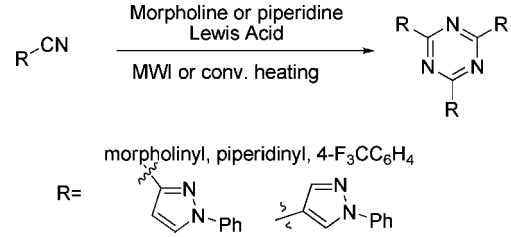
Mizuno et al. reported an organic-free process for the synthesis of several 1*H*-quinazoline-2,4-diones from the corresponding 2-aminobenzonitriles with $scCO_2$ as solvent and reactant in the presence of a catalytic amount of DBU or triethylamine (TEA) (Table 84).[607]

5.3. Containing Three Nitrogen Atoms

5.3.1. Solvent-Free Reactions

Symmetrically substituted 1,3,5-triazines can be prepared under SFC through the cyclotrimerization of nitriles in the presence of silica-supported Lewis acids ($ZnCl_2$, $AlCl_3$, and $TiCl_4$) as catalysts (Scheme 148). Microwave irradiation can

Scheme 148



lead to the best results in shorter times, although conventional heating leads to the best yields in 24 h, particularly when silica-supported zinc is employed. In this procedure, piperidine or morpholine should be used as nucleophile to induce the cyclotrimerization.[608] The cyclotrimerization of cyanopyrazoles can also be performed under conventional heating (200 °C) in presence of piperazine and yttrium trifluoromethanesulfonate as catalyst. However, this method has proven to be somewhat inefficient with respect to the isolated yields of the products (7−66%).[609]

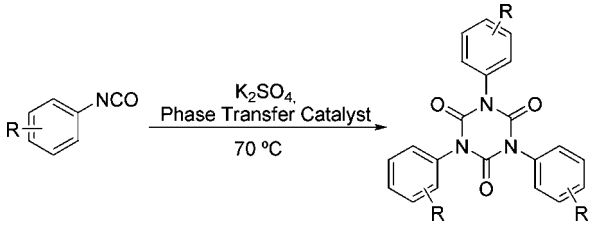
The preparation of substituted 1,3,5-triazines can also be done through modification of cyanuric chloride. Several N-heterocycles have been successfully employed as nucleophiles in the substitution reaction under MWI or conventional heating.[610] When amines are employed as nucleophiles toward chlorine substitution of cyanuric chloride or 2-chloro-4,6-di(dialkylamino)-1,3,5-triazines under microwave irradiation, symmetrical or asymmetrical melamines, respectively, can be obtained.[611,612]

From the cyclotrimerization of aryl isocyanates under solvent-free conditions at 70 °C, using potassium sulfate in catalytic amounts and a phase transfer catalyst (TBAB), isocyanurates can be obtained in good yields (Table 85). In order to improve the reaction rate, isocyanates containing electron-withdrawing groups should be used.[613]

For the preparation of thiazolo-*s*-triazines, thiazole Schiff bases, ammonium acetate, and aromatic aldehydes can be condensed under microwave irradiation. Regardless of the uncertainty about the reaction mechanism, which can go via conjugate addition of ammonia to the Schiff base or by a [4 + 2] cycloaddition, microwave irradiation leads to better yields than conventional heating conditions and also better diastereoselectivity (Table 86).[614]

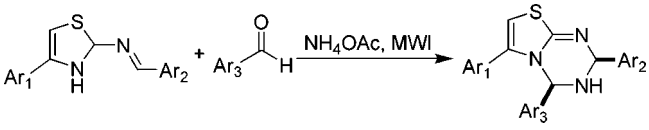
The analogues of 1,3,5-triazines, 1,2,4-triazines, can be efficiently prepared in a microwave oven through the reaction of phenacyl bromide derivatives with hydrazides in the presence of an inorganic support (Scheme 149). In the comparison of silica gel, montmorillonite K-10 clay, and

Table 85



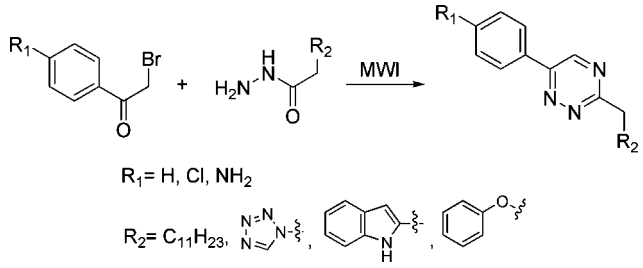
entry	R	time (min)	yield (%)
1	H	15	94
2	4-Cl	10	89
3	3,4-Cl	5	86
4	4-NO_2	4	84
5	4-AcO	14	91
6	4-MeO	68	96

Table 86



entry	Ar_1	Ar_2	Ar_3	time (min)	yield (%)	*cis*/*trans*
1	Ph	Ph	Ph	10	78	93:7
2	Ph	Ph	4-ClC_6H_4	8	84	94:6
3	Ph	4-$MeOC_6H_4$	Ph	12	75	93:7
4	Ph	4-$MeOC_6H_4$	4-ClC_6H_4	10	81	94:6
5	Ph	4-ClC_6H_4	Ph	8	83	93:7
6	Ph	4-ClC_6H_4	4-ClC_6H_4	6	89	95:5
7	4-MeC_6H_4	4-ClC_6H_4	Ph	10	82	94:6
8	4-MeC_6H_4	4-ClC_6H_4	4-ClC_6H_4	8	86	96:4
9	4-MeC_6H_4	4-ClC_6H_4	4-$MeOC_6H_4$	12	80	95:5

Scheme 149

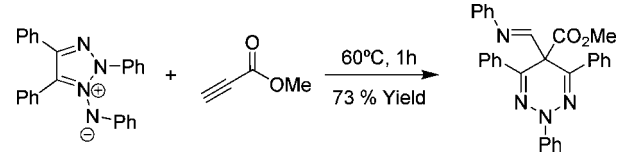


neutral alumina as supports, neutral alumina proved to be the most efficient in terms of reaction time/yield relationship.[615] In other hand, 3-amine-1,2,4-triazines can be prepared by cyclization of 1,2-bis(amidinohydrazone)s at 200 °C by conventional heating. This last method seems very interesting since, when the reaction is performed in a closed glass ampule the reaction product may be isolated after sublimation in the reaction vessel.[616] The 3-mercapto-1,2,4-triazine derivatives can be prepared by condensation of thiosemicarbazide with diketones through microwave irradiation in 6−7 min. Similarly, with DMAD or DEAD instead of the diketone, the compounds with a carbonyl and exocyclic double bonds can be obtained.[198]

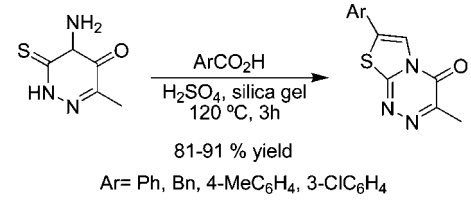
Despite the lack of synthetic procedures for the synthesis of 1,2,3-triazine derivatives, a method was reported for the preparation of fluorescent 2,5-dihydro-1,2,3-triazine. This molecule can be prepared in 73% yield through a conventional heating reaction of a 1,3-dipole triazolium derivative with methyl propiolate for 1 h (Scheme 150).[617]

A diasteroselective three-component synthesis can be adopted for the preparation of thiazolo-*s*-triazine *C*-nucleo-

Scheme 150



Scheme 151



sides through irradiation of a mixture of a thiazole Schiff base and an aldose in presence of ammonium acetate with microwaves. Remarkably, under MWI, this reaction proved to be much more diasteroselective than under conventional heating.[618] Through a one-pot condensation, triazin-5-ones can be condensed with an aromatic carboxylic acid in presence of sulfuric acid supported silica gel and further cyclized to yield thiadiazolo triazinones (Scheme 151).[619] Analogous to the reported reaction of 4-amino-5-methyl-3-thioxo-2*H*-1,2,4-triazole with aldehydes to form imine derivatives, 4-amino-6-methyl-5-oxo-3-thioxo-2*H*-1,2,4-triazine reacts with aromatic aldehydes yielding the corresponding imines in good yields (64−95%) through use of microwave conditions.[450]

5.3.2. Reactions in Ionic Liquids

Imidazo[1,2-*a*]pyrimidine derivatives are an important class of organic compounds that have been used as antimicrobial agents,[620,621] azo dyes,[622] and antagonistic agents.[623] Pharmaceutically useful compounds based on 2-arylimidazol[1,2-*a*]pyrimidines were synthesized using the ILs [bmim][BF_4], [emim][BF_4], and [bpyr][BF_4] as green, recyclable alternatives to conventional solvents[624,625] through cyclocondensation reactions of α-bromoacetophenones with 2-aminopyrimidine in good yields and selectivity.[626] Several bromoacetophenones containing different substituent groups (R), such as chloro, bromo, fluoro, nitro, methyl, methoxy, and phenyl, were tested with 2-aminopyrimidine in the presence of sodium carbonate to form corresponding 2-arylimidazo[1,2-*a*]pyrimidines in good yields (77−92%) and short reaction times (3−6 h) **(**Scheme 152**)**. The ILs could be recovered and reused at least six times without decrease in the yield of product.

More recently, Xie[627] reported a one-pot synthesis of 2-arylimidazo[1,2-*a*]pyrimidines by the reaction with ketones, [hydroxy(tosyloxy)iodo]benzene (HTIB), and 2-aminopyrimidine using the IL [bpy][BF_4] (Table 87).

Previously the author examined the efficiency of different ILs such as [bpy][BF_4], [bmim][BF_4], and [bmim][PF_6] in the cyclocondensation of α-tosyloxyacetophenone with 2-aminopyrimidine. The authors observed a dramatic effect over the reaction yield and time when IL [bpy][BF_4] was used (82% yield in 1 h at rt) comparing with the reaction performed in ethanol (70% yield in 6 h at 80 °C). In comparison with reported methods in the literature using organic solvents such as DMF, ethanol, and acetone,[624,625] the present methodology involving ILs has some advantages, particularly enhanced reaction rates, mild reaction conditions,

Scheme 152

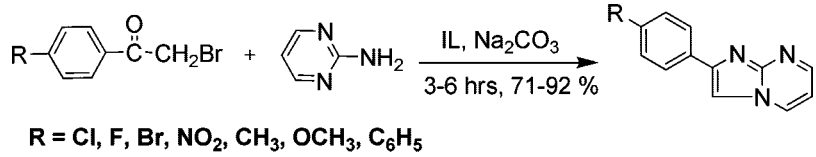
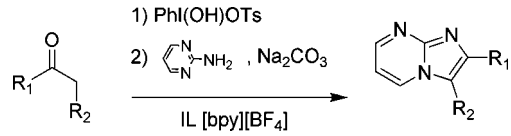
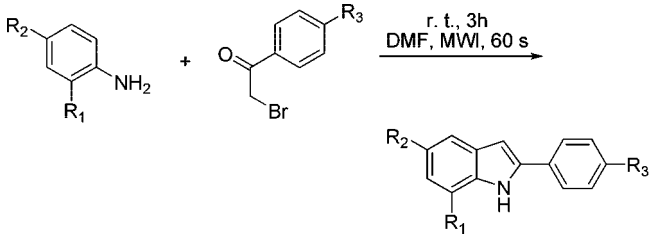


Table 87



entry	R_1	R_2	product	yield (%)
1	Ph	H	2-phenylimidazo[1,2-*a*]pyrimidine	80 (1st) 82 (2nd) 80 (3rd)
2	*p*-FC_6H_4	H	2-(4-fluorophenyl)imidazo[1,2-*a*]pyrimidine	85
3	*p*-ClC_6H_4	H	2-(4-chlorophenyl)imidazo[1,2-*a*]pyrimidine	83
4	*p*-BrC_6H_4	H	2-(4-bromophenyl)imidazo[1,2-*a*]pyrimidine	81
5	*p*-$CH_3C_6H_4$	H	2-(4-methylphenyl)imidazo[1,2-*a*]pyrimidine	75
6	*p*-$CH_3OC_6H_4$	H	2-(4-methoxyphenyl)imidazo[1,2-*a*]pyrimidine	72
7	Ph	Me	2-phenyl-3-methylimidazo[1,2-*a*]pyrimidine	76
8	furane	H	2-(2-furanyl)imidazo[1,2-*a*]pyrimidine	73

Table 88



entry	R_1	R_2	R_3	yield (%)
1	H	H	H	75
2	H	H	Cl	52
3	H	H	Me	54
4	H	Me	H	56
5	H	Cl	H	59
6	Me	H	H	67
7	H	Me	Me	57
8	H	Me	Cl	55
9	MeO	H	H	56

simple manipulation, easy isolation of product, and higher yields. Additionaly, the IL medium can be recycled without decrease of yield.

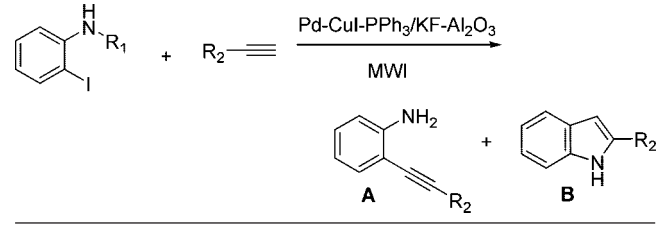
6. Indole-Based Heterocycles

6.1. Solvent-Free Reactions

The Bischler reaction is one of the most important methods for the preparation of indole heterocycles under classical conditions. Under solvent-free conditions microwave irradiation can also be successfully applied (Table 88). By this method, maintaining a mixture of phenacyl bromide derivatives and substituted anilines at room temperature for 3 h with further microwave irradiation in the presence of some drops of DMF (to improve the energy transfer), 2-arylindoles can be obtained in reasonable to good yields.[628]

In an attempt to promote the Sonogashira coupling between *o*-iodo-substituted protected anilines and terminal alkynes, another method for the preparation of 2-substituted indoles was observed. The cyclization was performed in the

Table 89



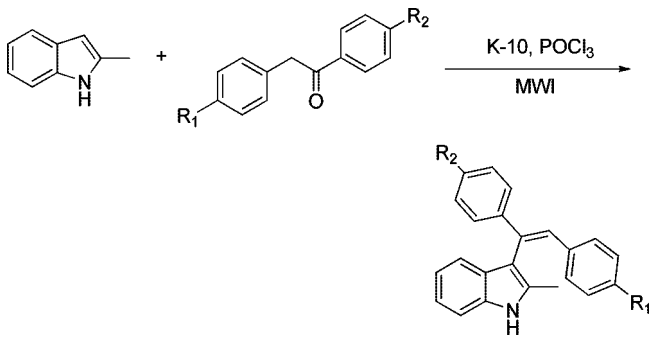
entry	R_1	R_2	yield (%)	ratio (**A**/**B**)
1	COMe	Ph	41	1:100
2	$COCF_3$	Ph	68	38:62
3	SO_2Me	Ph	80	0:100
4	$COCF_3$	4-MeC_6H_4	70	43:57

presence of potassium fluoride doped alumina, palladium powder, cuprous iodide, and triphenylphosphine in a microwave oven (Table 89).[629]

By condensation of benzylamine with isotin, azomethine ylide is formed and can be consequently reacted via 1,3-dipolar cycloaddition with bis-arylmethylidene cyclohexanones to yield dispiro oxindole derivatives. By this procedure, the reactants are simply ground together with K-10 montmorillonite under MWI for short times (40−80 s).[630] Similarly, this procedure can also be applied to the [3 + 2] cycloaddition of 9-arylidene fluorenes with the generated dipoles from isatin and secondary amino acids. The reaction can be performed in presence of K-10 clay or under neat conditions, affording the pyrrolo-oxindole derivatives with a spiro carbon in good yields (78−98%).[631] Recently, Baylis−Hillman adducts of ninhydrin were reported to undergo 1,3-dipolar cycloaddition with mono-, di-, and triketones under these conditions to afford spiro adducts.[632] The use of K-10 montmorillonite proved to be very fruitful when used as a catalyst in the microwave-induced condensation and further cyclization of 2,5-hexanedione with pyrrole or *N*-alkyl pyrroles. Despite the good to excellent yields obtained (75−98%), the method failed when electron-withdrawing N-substituents were used.[140]

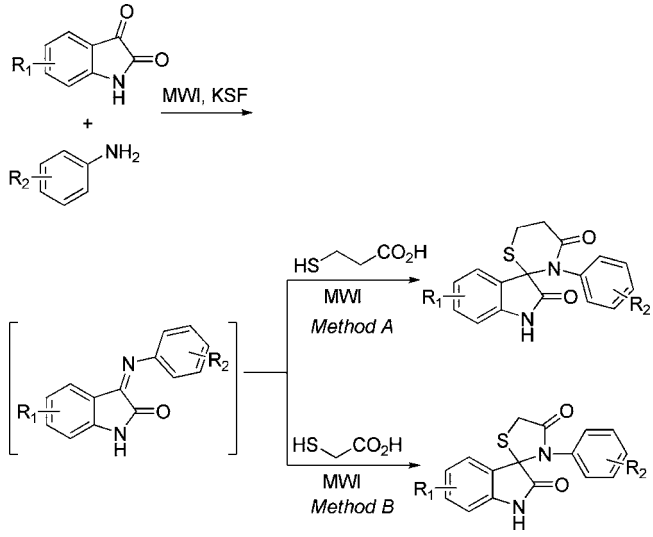
Regarding substituent introduction in indolic compounds, it was observed that a diarylvinyl group can be introduced

Table 90



entry	R_1	R_2	reaction time (min)	yield (%)
1	H	H	12	80
2	H	Me	9	82
3	H	MeO	7	88
4	Cl	H	10	81
5	Cl	Me	8	85
6	Cl	MeO	7	88

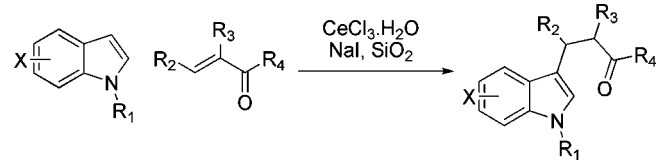
Table 91



method	R_1	R_2	yield (%)
A	5,7-Me_2	H	91
A	5,7-Me_2	4-CO_2H	92
A	5,7-Me_2	2-CO_2H	93
A	5,7-Me_2	3-Cl	90
A	5-Br	4-CO_2H	86
A	5-Br	2-CO_2H	88
A	5-Br	2-Cl	89
A	5-Me	4-Me	91
B	H	4-Cl	90
B	H	3-Cl	88
B	H	2-Cl	91
B	H	4-CO_2H	87
B	5,7-Me_2	4-Cl	92
B	5,7-Me_2	3-Cl	91
B	5,7-Me_2	4-CO_2H	89
B	5,7-Me_2	2-CO_2H	90
B	5-Br	3-Cl	87
B	5-Br	2-Cl	89
B	5-Br	4-CO_2H	85
B	5-Br	2-CO_2H	86
B	5-NO_2	4-F	85

in the highly reactive 3-position by reacting 2-methyl indole with benzyl aryl ketones in presence of montorillonite K-10 clay and phosphoryl chloride under MWI (Table 90).[633] In a similar way to the pyrrole ethynylation, indoles can be ethynylated through the reaction of 1-benzoyl-2-bromoacetylene in the presence of a 10-fold mass excess.[634] Methyl trifluoropyruvate was reported to react efficiently (57−98%) through Friedel−Crafts alkylation of indoles at the 3-position under solvent- and catalyst-free conditions after 1 min.[635] In a similar way, (3-indolyl)glycine derivatives can be synthesized at room temperature by condensation of glyoxylate, indole, and an amine.[636]

Table 92



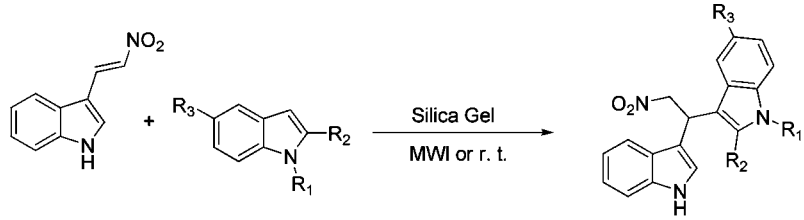
entry	X	R_1	R_2	R_3	R_4	time (h)	yield (%)
1	H	H	H	H	Me	2.0	96
2	H	H	H	Et	*n*-Bu	2.5	88
3	H	H	$CH_3(CH_2)_4$	H	Me	3.0	91
4	H	H	cyclohexanone			48	82
5	H	H	cyclopentanone			48	89
6	Br	H	H	H	Me	48	79
7	Br	Me	H	H	Me	7.5	85
8	NO_2	Me	H	H	Me	72	89
9	MeO	H	H	H	Me	1.5	89

A simple method for the reaction of indole with epoxides was recently developed by Azizi et al. through the use of lithium perchlorate as catalyst at 60 °C. The absence of solvent was seen to be necessary for success of the reaction, since the use of organic solvents lead to recovery of the starting material. The method was seen to be highly regioselective since the nucleophilic attack occurs at the less-substituted carbon of the epoxide.[637] Previously, indole derivatives were reported to react with oxiranes and aziridines on a silica surface at 70 °C in up to 76% yield.[638]

With the use of microwaves, *in situ* generated 3-arylamino-2*H*-indol-2-one derivatives can react with thioacids in a reaction of cyclocondensation to afford indolic spiro compounds in good yields (Table 91). Among several inorganic supports studied, montmorillonite KSF proved to be the best under these reaction conditions.[639] Recently, through the *in situ* formation of 3-(1-cyano-2-ethoxycarbonylethylidene)-2,3-dihydro-2-oxoindole by the Knoevenagel condensation of 1*H*-indole-2,3-dione and ethyl cyanoacetate under microwave irradiation, indole based spiro derivatives were synthesized after reaction with 4-hydroxycoumarin through Michael addition.[640] Spiro-[indole-pyrido[2,3-*d*]pyrimidines] were reported, by the same authors, to be formed by the reaction of the *in situ* generated [indole-dihydropyridine] and urea/CS_2 under microwave irradiation using basic alumina as solid support and a few drops of DMF.[641] Recently, spirooxindoles with fused chromenes were synthesized through the three-component condensation of isatin, malonitrile, and α-naphthol/*β*-naphthol using indium trichloride impregnated silica gel as a catalyst under microwave irradiation.[642]

$ZrOCl_2 \cdot 8H_2O$ was tested as catalyst for the addition of indoles to α,*β*-unsaturated ketones under solvent-free conditions at 50 °C. This method proved to be suitable for substituent introduction at the 3-position of indole in high yields and short reaction times (up to 2 h, 77−95% yield).[643] This catalyst was also observed to be suitable for the condensation of indoles with carbonyl compounds in order

Scheme 153



a: R_1= R_2= R_3 = H; **b**: R_1= Me, R_2= R_3= H; **c**: R_1= Me, R_2= H, R_3= Br; **d**: R_1= Et, R_2= R_3= H; **e**: R_1= *i*-Pr, R_2= R_3= H; **f**: R_1= R_3= H, R_2= Me; **g**: R_1= R_2= H, R_3= Br; **h**: R_1= R_2= Me, R_3= H

to synthesize bis(indolyl)methanes in good to excellent yields (75−94%).[644]

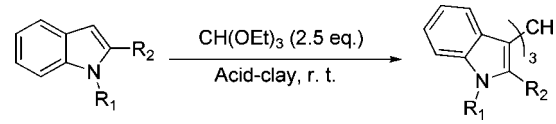
Regarding indole substituent modification, basic alumina and $CeCl_3 \cdot 7H_2O-NaI-H_2O$ supported on silica gel were found to be good catalysts for the conjugate addition of indoles to nitroalkenes.[645,646] However, when basic alumina is used, nitro alcohols can be used as nitroalkene equivalents since under the reaction conditions these compounds are dehydrated to the corresponding nitroalkene.[645] The $CeCl_3 \cdot 7H_2O-NaI-H_2O$ system supported on silica gel has also proven to be a good catalyst for the Michael addition of indole derivatives to α,β-unsaturated ketones affording the 3-(3-oxoalkyl)indoles in good yields (Table 92).[647] Recently, sulfamic acid was reported as a suitable catalyst for this transformation under conventional heating conditions (60 °C).[648]

A three-component reaction under solvent-free conditions through conventional heating at 80−120 °C was reported for the synthesis of 3-alkylated indoles. In this method, indole, aldehydes, and barbituric acid derivatives were reacted for 10−20 min at high temperatures in the absence of catalyst to favor the formation of aldol condensation product between the aldehyde and barbituric acid derivative and further Michael addition. The major side product was reported to be bisindolyl-methanes, particularly when barbituric acid was used instead of *N*,*N*-dimethylbarbituric acid.[649]

Similarly, the Michael reaction of indoles with 3-(2′-nitrovinyl)indoles for the synthesis of 2,2-bis(indolyl)nitroethanes (Scheme 153) can be performed at room temperature (69−84% yield) or through MWI (70−86% yield) of the mixture supported on TLC-grade silica gel. Interestingly, when column-grade silica is employed as support, the reaction does not occur, and it should be taken in account that when performed at room temperature the reaction takes a much longer time (8−14 h) than when performed in a microwave oven (7−12 min).[650,651] A thiourea-based organocatalyst has been developed for the reaction between nitroolefins and indole derivatives, leading to the 3-substituted indole derivatives in good yields (80−94%).[152] Molecular iodine can be used as catalyst for the Michael addition of enones with indoles without the use of any solvent. By this method, the 3-substituted indole is obtained in reasonable yields in 30 min at room temperature.[652]

Other methods to obtain bis(indolyl) compounds are by simple grinding of indole with aromatic aldehydes in presence of catalytic molecular iodine,[653] sulfamic acid,[654] silica sulfuric acid,[655] or $NaBF_4$[656] leading to the formation of bis(indolyl)methanes in good yields (72−96%) in a few minutes (5−45 min). Through a conventional heating procedure, ammonium chloride at 90 °C,[657] TiO_2,[658] and diammonium hydrogen phosphate[659] at 80 °C were also reported as efficient catalysts to obtain diindolylmethanes from indole and aldehydes or ketones. For the microwave version of this procedure, iron(III) chloride proved to be a good catalyst toward the electrophilic substitution of indoles.[660] Similarly, phosphoric acid on silica gel was also observed to promote the reaction of indoles with aldehydes to yield symmetrical bis(indolyl)alkanes at 60−70 °C,[661] while $LiClO_4$ was observed to efficiently catalyze the reaction without the inorganic support.[662] Montmorillonite K-10 clay can also be employed as catalyst of this reaction at room temperature or toward the synthesis of tris(indol-3-yl)methanes.[663,664] However, the use of triethyl orthoformate absorbed on acid clay in the synthesis of triindolylmethanes leads to better selectivity toward symmetrical compounds (Table 93).[665]

Table 93



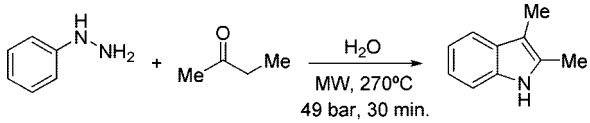
entry	R_1	R_2	time	yield (%)
1	H	H	<5 min	85
2	Me	H	<5 min	87
3	Et	H	<5 min	92
4	H	Me	2 h	74
5	Me	Me	2 h	82

The preparation of bis-indolizines under solvent-free conditions can be achieved in good yields (81−93%) by reacting 4,4′-bipyridinium diquaternary salts with acetylene carboxylates on potassium fluoride supported alumina under MWI.[666] As an example of indolic compounds, β-carbolines can be prepared by microwave-assisted Pictet−Spengler reaction of tryptamine or tryptophan derivatives with aldehydes supported on silica gel or by Bischler−Napieralski cyclization of *N*-formyltryptamine or *N*-acetyltryptamine.[667] Spiroindoline-1,4-dihydropyridines were reported to be prepared in excellent yields (78−97%) through the condensation of isatins, primary amines, ethyl cyanoacetate, and cyclohexanone on montmorillonite K-10 under microwave irradiation.[668]

6.2. Reactions in Aqueous Media

Regarding the synthesis of the indole heterocyclic structure, a study was recently presented in which the properties of water between 200−300 °C were explored; these conditions are generally known as near-critical water (NCW). Water at these temperatures has properties that maybe considered more favorable for organic synthesis. It has a density and polarity similar to those of acetonitrile at room temperature; furthermore, the dielectric constant of water drops rapidly with temperature and at 250 °C has fallen from 78.5 (at 25 °C) to 27.5.[669] Another

Scheme 154



Scheme 155

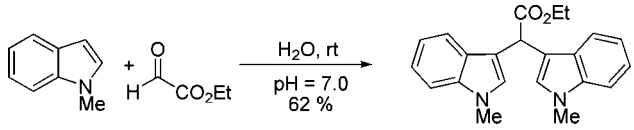
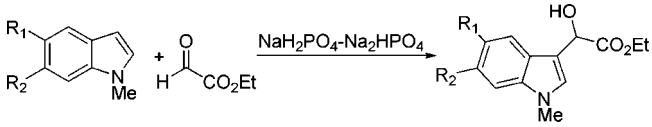
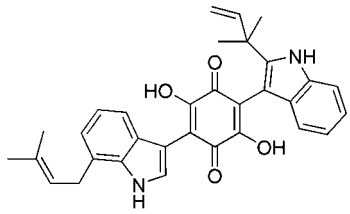


Table 94



entry	R_1	R_2	time (h)	pH	yield (%)
1	H	H	4	7.1	67
2	Me	H	4	6.8	84
3	H	Me	4	6.8	70
4	H	Cl	30	6.8	62

Scheme 156



Demethylasterriquinone B1

important particularity of water at these temperatures is that the ionic product (dissociation constant) increases considerably. At 250 °C, this constant has increased by 3 orders of magnitude compared with the room temperature value. Therefore, NCW can act as an acidic, a basic, or an acid−base catalyst.[669]

Taking advantage of NCW properties and combining it with microwave-assisted technologies, Kappe et al. succeeded in the preparation of 2,3-dimethylindole (Scheme 154).[669] The reaction of phenylhydrazine and butanone at 270 °C resulted in complete conversion of phenylhydrazine and 64% isolated yield of 2,3-dimethylindole.[669]

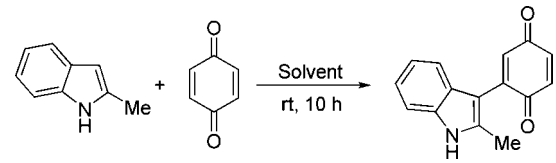
The *N*-methylindole reacted with ethyl glyoxylate affording the 2,2-bis(indolyl) product, which resulted from a double addition to the carbonyl reactant (Scheme 155).[202]

Different indoles were submitted to this transformation affording reasonable to excellent yields of alkylated products. This reaction series was carried out using a buffer solution of 1 M $NaH_2PO_4-Na_2HPO_4$ (Table 94).[202]

In a recent report, with the final objective of synthesising biologically active molecules such as the insulin mimetic demethylasterriquinone B1 (Scheme 156), Li et al. disclosed the direct coupling of indole compounds with 1,4-benzoquinones. This transformation was achieved with remarkable success without the use of any catalyst, additive, or organic solvent.[670]

The reaction of 2-methylindole proceeded with a considerable water acceleration effect even though the reactants were incompletely solubilized compared with homogeneous organic systems. This observation is in line with previously

Table 95



entry	solvent	yield (%)
1	CH_2Cl_2	13
2	CH_2CN	not detected
3	Et_2O	not detected
4	THF	not detected
5	toluene	traces
6	C_2H_5OH	38
7	THF/H_2O (1:2)	55
8	C_2H_5OH/H_2O (10:1)	51
9	H_2O	82

reported "on water" effects (Table 95). According to the authors, it is possible that one of the reactants is slightly soluble in water and this reacts with the insoluble reagent on the surface of the solid. This suspension proved to be beneficial for the final reaction outcome, and the addition of an aqueous solution of LiCl (2.5 mL) or glucose (1 M in water) neither changed the yield obtained in water nor accelerated the reaction.[670]

A detailed study covering an extensive array of substrates was conducted by the authors, after which the methodology was applied to the synthesis of target molecules. The second coupling in water was achieved in moderate to high yields (68−92%) for all the substrates tested (Scheme 157).[670]

Indolizines are the key intermediates for a broad range of biologically important alkaloids. The methods used in their preparation are classified mainly as condensation and 1,3- or 1,5-dipolar cycloadditions. The second method is widely used and based on the reaction of pyridinium ylides with electron-poor alkenes and alkynes.

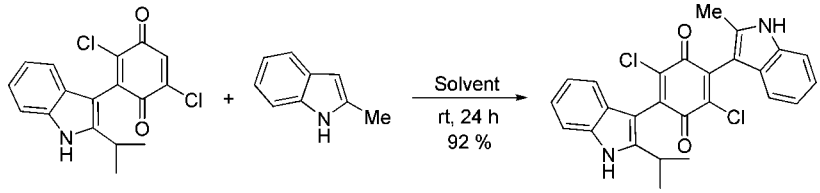
The preparation of indolizines in water was recently disclosed by Liu et al. using a multicomponent coupling/cycloisomerization catalyzed by gold(III).[671] The authors proposed a mechanism based on a gold-catalyzed three-component coupling via a Mannich−Grignard reaction followed by nucleophilic attack of the nitrogen lone pair to the activated triple bond. Deprotonation followed by demetalation afforded the desired indolizine. This methodology rapidly provided access to substituted aminoindolizines in moderate to good yields (Scheme 158).

6.3. Reactions in PEG or PEG Tag Approaches

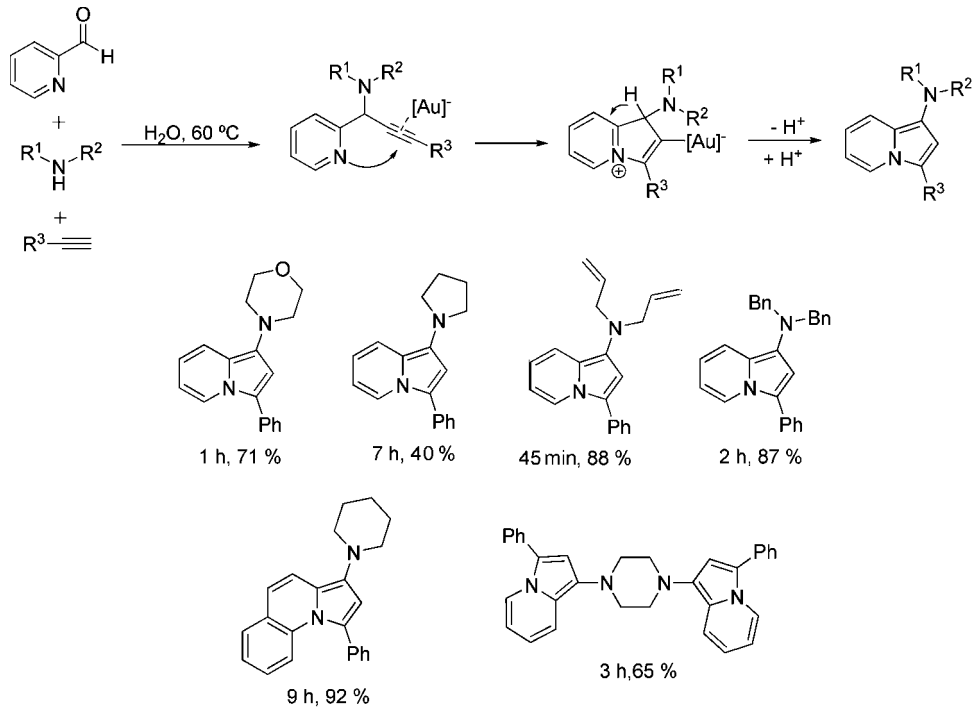
The tetrahydro-β-carboline nucleus is found commonly in a large number of tryptophan-derived natural product alkaloids. These classes of heterocycles could be readily obtained by a cyclocondensation of tryptophan with several aldehydes and ketones (Pictet−Spengler reaction). Sun et al. shown that it was possible to prepare a large library of these classes of compounds using soluble-PEG-phase synthesis in high yields (generally above 90%, Scheme 159). Interestingly, the traditional excess of trifluoroacetic acid was not required to promote this transformation. For these polymer-supported target molecules, catalytic amounts of p-TSA were enough. After cleavage from the soluble support the desired heterocycles showed good purity (>70%).[672]

Chen et al. reacted $BrCH_2COBr$ with PEG (MW = 3400) and pyridine to obtain polymer-supported pyridinium ylides. The respective target molecules were prepared in high yields

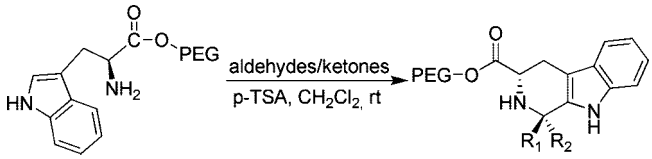
Scheme 157



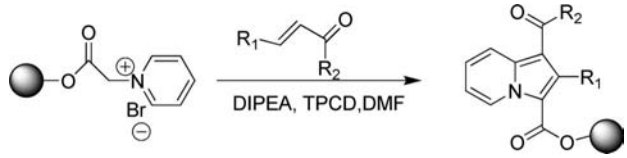
Scheme 158



Scheme 159



Scheme 160



(>80%, after cleavage) in the reaction with α,β-conjugated alkenes (Scheme 160).[673] If quinolinium ylides were prepared instead of pyridinium ylides, a library of pyrrolo[1,5-α]isoquinolines could be obtained, though in moderate yields (50−80%, after cleavage).[674]

6.4. Reactions in Ionic Liquids

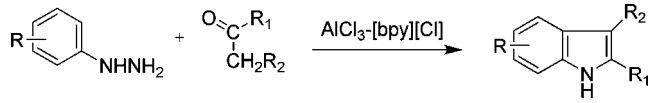
The efficient regioselective alkylation of the ambident nucleophiles indole is usually achieved by preformation of the ambident indolyl anions[675] and subsequent treatment with alkyl halide. In 1998, Seddon et al.[676] described the possibility to use ILs [bmim][PF_6] and [bmim][BF_4] as an attractive clean synthetic alternative to classic dipolar aprotic solvents for alkylation of ambident nucleophiles. The reaction of indole with simple alkyl halides such as EtBr, BuBr, or MeI at room temperature was performed in IL [bmim][PF_6] using solid KOH as base, and the N-alkylated product was obtained almost exclusively in high yields (≥91%). This simple methodology has been described with some advantages including the ease of product isolation, the regioselectivity, and the potential for recycling. The Fisher indole synthesis of different cyclic and acyclic ketones[677,678] has been tested using 1-butylpyridinium chloride−$AlCl_3$ (molar ratio 23:67) as solvent as well as catalyst (Table 96).[679] The use of chloroaluminate ILs is an efficient alternative to catalytic reaction conditions such as $ZnCl_2$,[680] hot polyphosphoric acid (PPA),[681] or PCl_3[682] in organic solvents.

The amount of $AlCl_3$ required in the IL method is much lower than that of other reported catalysts like PPA and $ZnCl_2$. The versatility of this type of reaction has been demonstrated and applied in the synthesis of a number of biologically active natural and synthetic products including essential amino acids and antioxidant compounds.[683]

Jenkins et al.[684] observed the exclusive formation of 2,3-disubstituted indoles in high yields by the Fisher indole synthesis using 1 equiv of the IL choline chloride·$2ZnCl_2$. The corresponding products were isolated directly by vacuum sublimation from the selected IL. In the case of unsymmetrical dialkyl ketones, regiospecific formation of a single product was observed arising from the formation of the more substituted enamine intermediate.

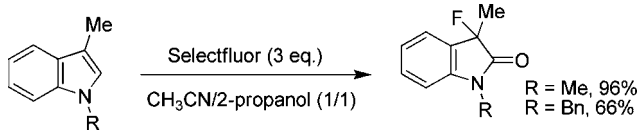
Electrophilic fluorination of indoles has been performed using ILs as solvent with high chemoselectivity and yields

Table 96



entry	R	ketone	indole	time (min)	yield (%)
1	H	acetophenone	2-phenylindole	60	73
2	H	butan-2-one	2,3-dimethylindole	40	80
3	H	propiophenone	2-phenyl-3-methylindole	180	80
4	H	cyclohexanone	1,2,3,4-tetrahydro-indole	35	92
5	H	phenylacetone	2-methyl-3-phenylindole	40	44
6	H	4-methylacetophenone	2-(4-tolyl)indole	60	42
7	H	4-chloroacetophenone	2-(4-chlorophenyl)-indole	180	41
8	*p*-CH_3	acetophenone	2-phenyl-5-methylindole	60	78
9	*p*-CH_3	butan-2-one	2,3,5-trimethylindole	45	90
10	*p*-CH_3	cyclohexanone	1,2,3,4-tetrahydro-6-methyl-carbazole	30	90
11	*p*-Cl	cyclohexanone	1,2,3,4-tetrahydro-6-chloro-carbazole	35	92

Scheme 161



observed.[685] The best conditions described require the use of commercial Selectfluor and ethanol or methanol as cosolvent in order to minimize the protonated corresponding oxoindole (Scheme 161).[686,687] When applied to N-alkylated compounds, the use of 2-propanol led to high transformation into the desired fluorinated product, especially for the *N*-methyl substrate.

Substantially different results were observed in the presence of thiols.[685] When only 2 equiv of thiol is used, the fluorinated oxoindole is obtained in 63% yield, while the reaction stopped at the intermediate thio-substituted indole species in good yield (92%) if an excess of thiol was added (Scheme 162).

Yeung et al. developed a practical and convenient protocol for the Friedel−Crafts-type acylation of the C3 position of indoles that is promoted by acidic imidazolium chloroaluminate ILs (Scheme 163).[688] This methodology appears to be more general for less electron-rich indole ring systems, allowing good to high yields and no side products of over acylation observed.

It can be applied to the preparation of multiple-point pharmacophores of indoles substituted at different positions with versatile functionalities (e.g., CN, NO, CO_2H, Br, C═O, anisole, furan, and enolizable α-protons), which can lead to considerable chemical diversity.

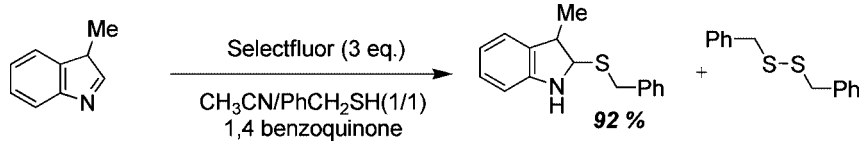
Efficient electrophilic substitution reactions of indoles with several aliphatic and aromatic aldehydes proceed smoothly in ILs using Lewis acids such as $In(OTf)_3$, $InCl_3$, $BiCl_3$, $ZnCl_3$, and YbCl to afford the corresponding bis(indolyl)-methanes in high yields.[689] Using $[C_8mim][PF_6]$ as the best IL and $In(OTf)_3$ as catalyst obtained the highest catalytic activity, and the reaction was completed in 15 min with 96% of yield (Table 97). When a weaker Lewis acid such as $ZnCl_2$ was used, it always required longer reaction times and an increase of the amounts of catalyst. The catalytic activity of $In(OTf)_3$ in IL gradually decreased in the second and third cycles, and no product formation was observed in fourth cycle. However, new addition of catalyst in the recycled IL allowed a performance similar to the one obtained in the first cycle.

More recent, Ji et al. described a green alternative protocol for electrophilic substituition reactions of indoles with several aldehydes using acidic task-specific ILs to afford the corresponding bis(indolyl)methanes in excellent yields.[690] The cause of this phenomenon may be explained by the acidity of these ILs. The best results were obtained with IL $[C_6mim][HSO_4]$ as catalyst and ethanol as solvent. This catalytic system can be reused at least five times without considerable loss of activity (Table 98). The authors tested this methodology using several aromatic and aliphatic aldehydes, which reacted smoothly with indole in high yields (80−99%). The reaction is highly chemoselective, reacting only with aldehydes but not with ketones.

Cheng et al.[691] first reported the reaction of indole with aldehydes and ketones in ILs using dysprosium triflate, $Dy(TfO)_3$, as the catalyst instead the lanthanide triflate normally described as useful and efficient for many electrophilic substitution reactions of indole with a variety of carbonyl compounds and imines. Initially the authors performed the reaction of indole with hexanal as model reaction using IL $[bmim][BF_4]$ and 2 mol % $Dy(TfO)_3$ affording the desired bis-indolyl product in 95% of yield in 1 h (Table 99). In comparison, the same reaction conducted in aqueous ethanol with 10 mol % $Dy(TfO)_3$ only yielded 84% after 24 h.[692] This process could be applied to a variety of aromatic and aliphatic aldehydes and ketones in high yields (76−98%) and short reaction times. The use of IL methodology allows the product to be easily separated from the catalyst as well as the reuse of the catalyst several times with reduced loss of catalytic activity.

Similarly, the reaction of indole with *N*-benzylidene aniline was analyzed in the presence of $Dy(TfO)_3$ (5 mol %) as catalyst and IL $[bmim][BF_4]$ as solvent. The reaction was completed after 10 h at room temperature affording a secondary amine 3-(phenylamino benzylidene) indole as

Scheme 162



Scheme 163

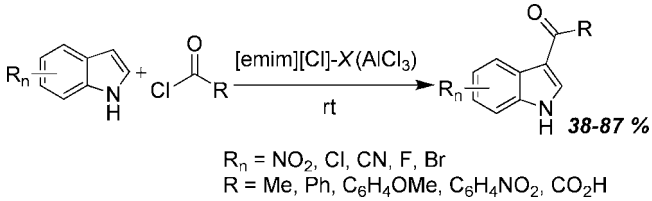
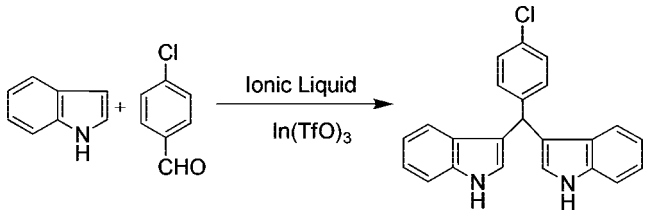


Table 97



entry	ionic liquid	Lewis acid (mol %)	time (min)	yield (%)
1	[bmim][PF_6]	$In(TfO)_3$ (5)	15	89
2	[C_6mim][PF_6]	$In(TfO)_3$ (5)	15	95
3	[C_8mim][PF_6]	$In(TfO)_3$ (5)	15	96 (1st)
			2880	87 (2nd)
			2880	42 (3rd)
			2880	0 (4th)
4	[C_{10}mim][PF_6]	$In(TfO)_3$ (5)	60	82
5	[bmim][BF_4]	$In(TfO)_3$ (5)	15	81
6	[C_6mim][Cl]	$In(TfO)_3$ (5)	720	0
7	[C_8mim][PF_6]	YCl_3 (5)	240	87
8	[C_8mim][PF_6]	$BiCl_3$ (10)	90	93
9	[C_8mim][PF_6]	$InCl_3$ (10)	60	71
10	[C_8mim][PF_6]	$ZnCl_2$ (10)	420	79

desired product (30%) and phenyl bis-indolyl methane as the byproduct (45%) (Table 100). Compared with the same reaction in EtOH/H_2O, the reaction in IL showed an enhanced reactivity but with the formation of a byproduct, bis-indolyl methane. The IL [bpy][BF_4] gave the best results in terms of yield and secondary indolyl amine produced. For all imines tested using $Dy(TfO)_3$ as catalyst in IL [bpy][BF_4], the reaction afforded secondary indolyl amines with moderate yields, along with significant amounts of byproduct bis-indolyl methanes.

Yadav et al.[693] have described a clean and efficient method for the conjugate addition of indoles to α,β-unsaturated ketones in the presence of copper(II) triflate (10 mol %) immobilized in IL [bmim][BF_4] as a novel and recyclable catalytic system (Scheme 164). The enones showed enhanced reactivity in ILs thereby improving the yields (82−95%) and reducing the reaction times (2−6 h) significantly. The recovery of the $Cu(OTf)_2$ catalyst was facilitated by the presence of the IL for five cycles without loss of activity.

6.5. Reactions in Fluorinated Fluids

The fluorous liquid-phase extraction (F-LPE) approach has been used elegantly by Curran et al. for tin radical chemistry based on the synthesis of highly fluorinated tin hydrides, which present high affinity for the fluorous phase, allowing the recovery of tin-based products, which are toxic and difficult to separate. In Table 101, one example of application of this methodology for the synthesis of aniline derivatives by *5-exo*-trig cyclization using the catalytic tin hydride approach is presented.[694]

Chich et al. extended the use of fluorous aryl selenyl chloride to the important formal dehydrogenation of carbonyl

Table 98

entry	IL catalyst (mol %)	solvent	time (h)	yield (%)
1	[C_6mim][HSO_4] (20%)	THF	22	99
2	[C_6mim][HSO_4] (20%)	DMF	40.5	99
3	[C_6mim][HSO_4] (20%)	DCM	7	89
4	None	MeCN	133	0
5	[C_6mim][BF_4] (20%)	MeCN	138	0
6	[acmim][Cl] (20%)	MeCN	72	70
7	[C_6mim][HSO_4] (20%)	MeCN	9	99
8	[C_6mim][HSO_4] (20%)	MeOH	1	90
9	None	EtOH	72	0
10	[C_6mim][BF_4] (20%)	EtOH	50	0
11	[acmim][Cl] (20%)	EtOH	47	74
12	[C_6mim][HSO_4] (20%)	EtOH	2.5	96
13	[C_6mim][HSO_4] (10%)	EtOH	3	96 (1st)
			4	93 (2nd)
			5	99 (3rd)
			6	98 (4th)
			8	99 (5th)
			10	96 (6th)
14	[C_6mim][HSO_4] (5%)	EtOH	3.5	99
15	[C_6mim][HSO_4] (1%)	EtOH	6	96

compounds to their α,β-unsaturated derivatives. Treatment of the crude reaction mixture with sodium metabisulfite allows the formation of toxic fluorous diaryl diselenide, which can be efficiently recovered by continous fluorous extraction.[695] This approach has been applied to the synthesis of pyrrolo-indole described in Scheme 165.

Starting from fluorous L-α-amino esters, Sun et al. synthesized 15 analogues of pharmacologically active tetrahydro-β-carbonylhydantoins starting from fluorous Boc-protected L-tryptophan ester (Scheme 166).[696]

Kondo et al. described a fluorous sulfonamide as an effective protecting group for the synthesis of a range of bisindoles from fluorous indolylboron and dihaloaromatics via palladium-catalyzed coupling reaction. In Scheme 167, one example is presented in which the product was isolated by F-SPE.[697] The authors extended the fluorous indole unit to α-lithiation and reaction with different aldehydes.[698] This methodology was efficiently explored for the synthesis of the bis(indole) alkaloid yuehchukene in six steps in which F-SPE was used in three steps (Scheme 168).

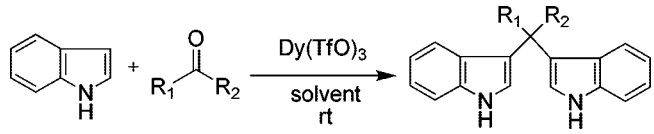
7. Benzo-Fused Six-Membered Rings

7.1. Containing One Nitrogen Atom

7.1.1. Solvent-Free Reactions

The most used method for the synthesis of quinolines is probably the Friedländer condensation. This method can be applied to solvent-free conditions using several substrates as well several catalysts or even without catalyst. Furthermore, it can be used under microwave irradiation or conventional heating. For instance, the preparation of polysubstituted quinolines can be successfully achieved in 85−96% yields at 100 °C or under MWI conditions by condensation of 2-aminoarylketones or 2-aminoarylaldehydes with ketones or aldehydes in the presence of p-TsOH (1 equiv) (Scheme 169). Although several acids can be used, p-TsOH proves to be very efficient concerning the extent of reaction and simplicity of work-up procedure.[699] In the same way, sulfuric acid can be used as catalyst in the microwave-assisted synthesis of quinolines[700] or can be supported on silica and used as catalyst in the reaction driven by conventional heating.[701] Recently, Zolfigol and co-workers reported a method where silica sulfuric acid was used as

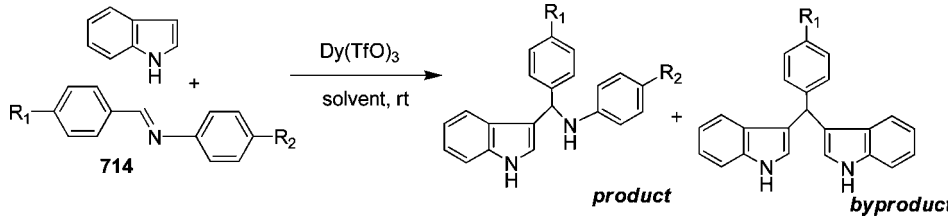
Table 99



entry	R_1	R_2	$Dy(TfO)_3$ (mol %)	solvent	time (h)	yield (%)
1	*n*-hexyl	H	10	EtOH/H_2O (2:1)	24	84
2	*n*-hexyl	H	2	[bmim][BF_4]	1	95 (1st) 94 (2nd) 92 (3rd) 91 (4th) 91 (5th) 90 (6th)
3	*n*-hexyl	H		[bmim][BF_4]	1	*a*
4	*n*-hexyl	H	2	[bmim][BF_4]	1	88
5	*n*-hexyl	H	2	[bpy][BF_4]	1	89
6	phenyl	H	2	[bmim][BF_4]	1	98
7	*p*-ClC_6H_4	H	2	[bmim][BF_4]	1	96
8	*p*-$MeOC_6H_4$	H	2	[bmim][BF_4]	1	99
9	methyl	methyl	10	EtOH/H_2O (2:1)	24	76
10	methyl	methyl	5	[bmim][BF_4]	24	96
11	methyl	methyl	5	[bmim][PF_6]	24	94
12	methyl	methyl	5	[bpy][BF_4]	24	98
13	pentyl	pentyl	5	[bmim][BF_4]	24	96
14	phenyl	methyl	10	[bmim][BF_4]	24	88

[a] No reaction.

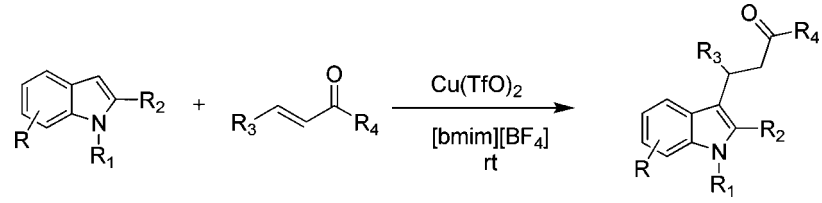
Table 100



entry	R_1	R_2	$Dy(TfO)_3$ (mol %)	solvent	time (h)	product (%)	byproduct (%)
1	H	H	10	EtOH/H_2O (4:1)	24	57	12
2	H	H	5	[bmim][BF_4]	10	30	45
3	H	H	5	[bmim][PF_6]	10	30	55
4	H	H	5	[bpy][BF_4]	10	47	45
5	H	H		[bpy][BF_4]	10	*a*	
6	Cl	H	5	[bpy][BF_4]	10	43	42
7	Cl	Cl	5	[bpy][BF_4]	10	53	37
8	CH_3	Cl	5	[bpy][BF_4]	10	48	52
9	CH_3	OCH_3	5	[bpy][BF_4]	10	37	45

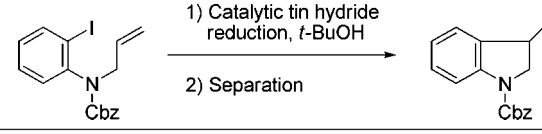
[a] No reaction.

Scheme 164



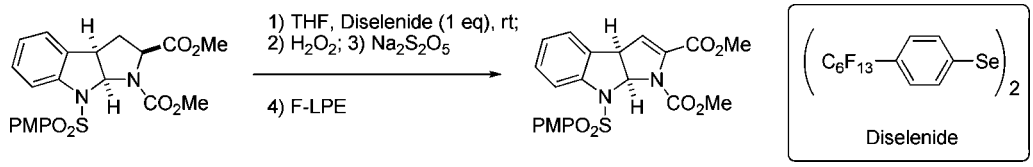
catalyst of this reaction under MWI, resulting in the formation of the desired quinolines in good to excellent yields (75−94%), for a wide range of ketones used.[702] If diketones are used as the carbonyl compounds, $NaHSO_4-SiO_2$ and trifluoracetic acid were observed to be good catalysts for the formation of quinolines after 1 h or 7−15 min, respectively, at 100 °C.[703,704] In the case of the microwave-induced version of Friedländer condensation, diphenylphosphate also proved to be effective for the condensation of acetophenones with 2-aminoacetophenone or benzophenone.[705]

Table 101

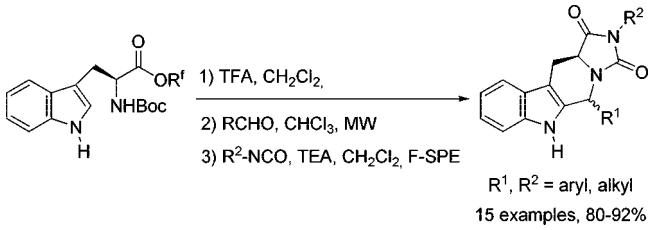


entry	tin hydride	separation	yield (%)
1	$(C_4F_9CH_2CH_2)_3SnH$	liquid−liquid	91
2	$(C_6F_{13}CH_2CH_2CH_2)_3SnH$	liquid−liquid	89
3	$(C_4F_9CH_2CH_2CH_2)_3SnH$	liquid−liquid	82
4	$(C_4F_9CH_2CH_2CH_2)SnH$	solid−liquid	75

Scheme 165



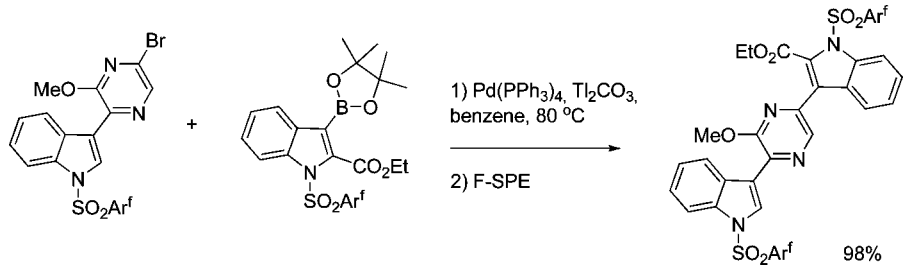
Scheme 166



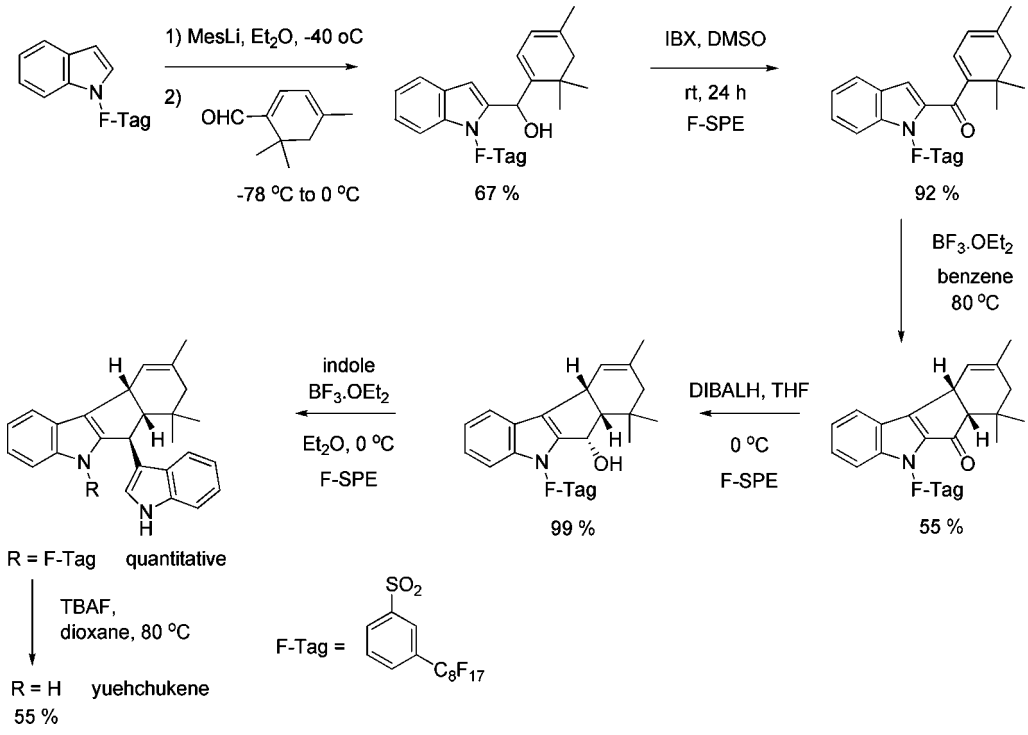
A modified version of this reaction can be also employed for the synthesis of these compounds. The coupling of 2-amino benzyl alcohol with ketones can be catalyzed by $[IrCl(cod)]_2$ or even by $IrCl_3$ in the presence of a base and a catalytic amount of PPh_3 (for yield improvement) at 100 °C.[706] Analogously, $RuCl_2(DMSO)_4$ was recently reported to catalyze this reaction; furthermore, primary and secondary alcohols can be used as ketone or aldehyde electrophilic partners in the presence of KO*t*-Bu. The high activity of this ruthenium complex was attributed to the excellent activity both as a hydrogen-transfer catalyst and as a Lewis acid, and benzophenone is needed for the regeneration of the active complex.[707]

A one-pot procedure for the synthesis of 2,4-disubstituted quinolines through the use of montmorillonite clay impregnated with 30 mol % copper(I) bromide has been developed. This procedure affords the desired quinolines in good to excellent yields under conventional heating or MWI by cyclization of terminal alkynes with generated *in situ* aromatic imines (Table 102).[708] Similarly, 2-pentafluorophenyl-substituted quinolines can be obtained by this procedure under MWI by reacting pentafluorobenzaldehyde, anilines, and alkynes in presence of montmorillonite clay impregnated with 30 mol % of CuBr.[709] Another one-pot procedure for the synthesis of polysubstituted quinolines by microwave induction involves the condensation of anilines and α- or *β*-monosubstituted alkyl vinyl ketones on the surface of silica gel impregnated

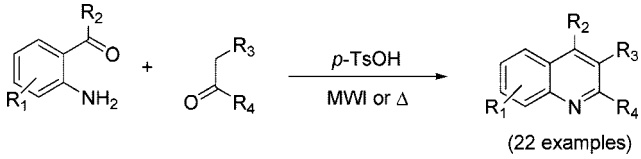
Scheme 167



Scheme 168



Scheme 169



with indium(III) chloride (30 mol %).[710,711] In case of halogenated quinolines, 7-chloro-6-fluoro-quinoline derivatives have been synthesized and modified through the use of microwaves and alumina as support. For instance, the introduction of a thiadiazole or oxadiazole in position 6 of the halogenated quinoline can be achieved in good yields.[712] Recently, using $SnCl_2 \cdot 2H_2O$ as reductant, 2-aminoarylaldehydes were replaced by 2-nitroarylaldehydes in the microwave-induced condensation with enolizable ketones.[713] Analogously, β-nitrovinylcarbazole derivatives can react with 2-aminoacetophenone at 40 °C in the presence of DABCO in order to synthesize 3-(3-nitroquinolyl)carbazoles. Through this procedure, 3-chromenylcarbazoles can also be synthesized if 2-hydroxybenzaldehyde is used as the nucleophile.[714]

For the preparation of styrylquinolines derivatives, an efficient protocol was developed for the microwave-induced reaction without the use of any inorganic support (Table 103). Starting from quinaldine derivatives with 2 equiv of aryl aldehyde, the desired product can be obtained in good yields and only 4 min of reaction time. This procedure allows the use of smaller quantities of aldehyde, since in the conventional heating reaction 6 equiv of aldehyde was needed to achieve the same results in 5 h.[715]

Several annulated quinoline derivatives such as quinolizine-, indolizine-, and pyrido-1,4-oxazine-fused quinolines were recently prepared through a three-component reaction. The reaction consisted in the condensation of equimolar amounts of 2-chloro-3-formyl quinolines, a cyclic amine, and an alkyl nitrile at 110−120 °C for 5 h (Table 104). This method was seen to be suitable for the preparation of these types of compounds but with a spirocyclic ring system if the nitrile was substituted by barbituric acids.[716]

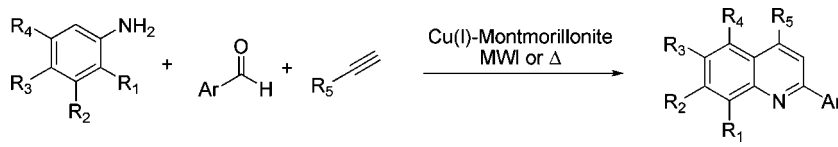
The preparation of quinophthalones can be achieved through the condensation of anhydrides and quinoline derivatives by microwave irradiation in presence of silica gel as catalyst. This inorganic support proved to be the best among others (alumina, montmorillonite K-10 clay) yielding the desired compounds in good to excellent yields (Table 105).[717] A fused imide with a quinoline ring can also be prepared under MWI and solvent-free conditions by reaction of a fused quinoline anhydride with a primary amine in wet K-10 clay,[718] while the quinoline-related acridines can be obtained by reaction of dicarboxylic acids or arylacetic acids with diphenylamine in a microwave oven, with zinc(II) chloride in high excess.[719]

For the preparation of dihydroquinolines, there are three methods that can be successfully employed. In parallel with the synthesis of quinolines by condensation of anilines and alkyl vinyl ketones on the surface of indium immobilized on silica gel, the use of β-disubstituted carbonyl compounds can lead to the formation of dihydroquinolines in reasonable yields under microwave irradiation.[710] Under conventional heating conditions, 3-nitro-1,2-dihydroquinolines (Table 106, entries 1−6) and also 3-nitrochromenes (Table 106, entries 7−l2) can be prepared by reaction of conjugate nitroalkenes with 2-aminobenzaldehyde or salicylaldehyde, respectively, using 1 g of γ-alumina per millimole of substrate (Table 106).[720] More saturated quinolines like octahydroquinoline can be prepared by microwave-induced reaction of Meldrum's acid, dimedone, ammonium acetate, and an aromatic aldehyde without the use of any inorganic support.[721] Recently, bismuth triflate was reported to be a suitable catalyst for the room-temperature preparation of 2,2,4-trimethyl-1,2-dihydroquinolines through the condensation of 2,2-dimethoxypropane with aryl amines. Despite good yields in the formation of dihydroquinolines (82−90%), the use of *o*-phenylenediamines led to the exclusive formation of 1,5-benzodiazepines (81−92%).[722]

An efficient procedure for the preparation of quinolones or 4*H*-1,4-benzothiazines through microwave-induced cyclization of *S*,*N*-acetals with potassium carbonate can be used affording the desired compounds in good to excellent yields (Scheme 170).[723]

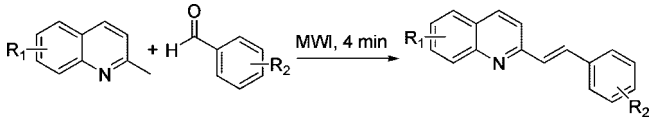
Quinolones can be prepared by a more interesting sequence of three steps in a completely solvent-free synthesis. The first step consists of the formation of an alkoxymethylene derivative by microwave-induced condensation of triethyl orthoformate with an activated methylene derivative. After reaction of the alkoxymethylene with an aromatic amine in

Table 102



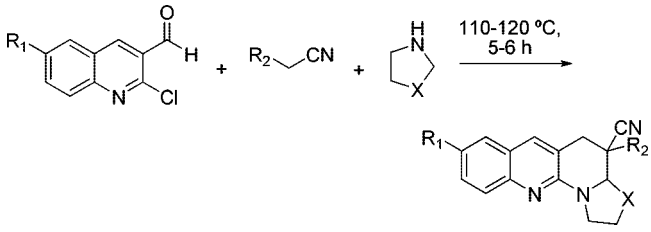
entry	R_1	R_2	R_3	R_4	Ar	R_5	yield under MWI (%)	yield under conventional heating (%)
1	H	H	H	H	Ph	$HOCH_2CH_2$	92	89
2	F	H	F	H	Ph	$HOCH_2CH_2$	89	85
3	H	H	H	H	$2,5\text{-}(MeO)_2C_6H_3$	$HOCH_2CH_2$	90	87
4	F	H	F	H	$4\text{-}FC_6H_4$	$HOCH_2CH_2$	87	81
5	H	H	H	H	$2,5\text{-}(MeO)_2C_6H_3$	$HOCH_2$	92	90
6	H	H	Me	H	$4\text{-}FC_6H_4$	$HOCH_2$	88	83
7	H	Cl	F	H	Ph	$HOCH_2$	86	80
8	H	H	MeO	H	$2,5\text{-}(MeO)_2C_6H_3$	$HOCH_2$	91	87
9	H	MeO	MeO	MeO	Ph	$HOCH_2$	93	89
10	H	H	H	H	$4\text{-}BrC_6H_4$	$HOCH_2$	85	82
11	H	H	Me	H	Ph	$HOCH_2$	89	86
12	H	MeO	MeO	MeO	Ph	Ph	92	89
13	H	H	Me	H	Ph	*n*-Bu	75	71
14	H	Cl	F	H	$4\text{-}FC_6H_4$	$HO\text{-}(CH_2)_5$	89	85

Table 103



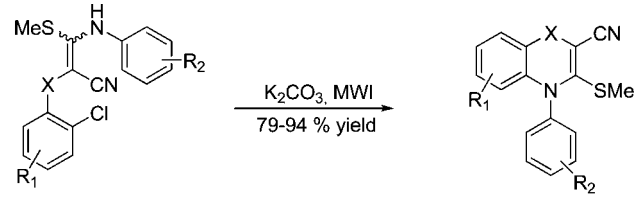
entry	R_1	R_2	yield (%)
1	8-CO_2H	2-Cl	75
2	8-CO_2H	2-OH	73
3	8-CO_2H	3-Br	65
4	6-CO_2H	2-OMe	59
5	5-CO_2H	2-OH	70
6	5-CO_2H	3-Cl	72
7	6-CO_2H	2-OH	75
8	7-CO_2H	3-Cl	30
9	5-CO_2H	2-Br	76
10	5-CO_2H	2-OMe	75
11	5-CO_2H	3-OMe	80
12	7-CO_2H	2-OMe	63
13	7-CO_2H	2-OH	62
14	5-CO_2H, 8-CO_2H	2-OMe	82
15	6-CO_2H	4-OMe	78
16	5-CO_2H, 8-CO_2H	3-Cl	75
17	6-CO_2H	2-Br	75

Table 104



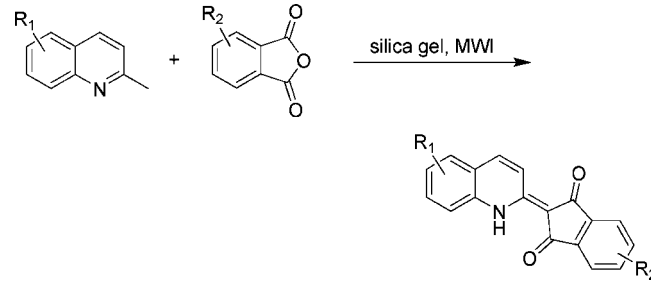
entry	R_1	R_2	X	yield (%)
1	H	Me	$(CH_2)_2$	54
2	Me	CN	CH_2	57
3	OMe	CN	CH_2	52
4	H	CO_2Et	$(CH_2)_2$	45
5	H	CN	CH_2	58
6	Me	CN	CH_2	60
7	OMe	CN	CH_2	55
8	H	CO_2Et	CH_2	45
9	H	CN	OCH_2	51
10	Me	CN	OCH_2	58

Scheme 170



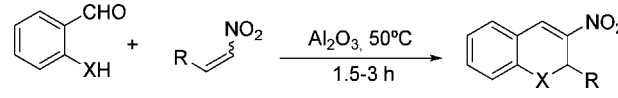
a microwave oven, in order to prepare the disubstituted aminoethylene, it can be submitted to cyclization under conventional heating (380 °C) by the Gould−Jacobs reaction[724] or in a microwave oven after immobilization on acidic alumina[725] (Scheme 171). Employing this acidic alumina,

Table 105



entry	R_1	R_2	yield (%)
1	H	H	97
2	H	4-Cl	95
3	H	5,6-$(COOOC)_2$	94
4	H	5,6-$(CO_2Me)_2$	91
5	4-Me	H	85
6	4-Ph	H	87
7	3-HO	H	86
8	3-HO	4-Cl	85
9	6-Me	H	93

Table 106



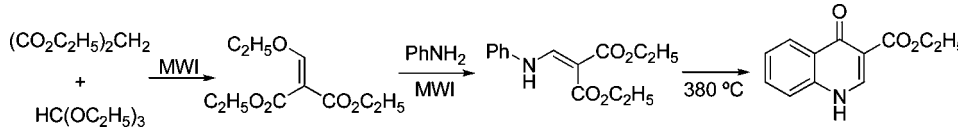
entry	R	X	reaction time (h)	yield (%)
1	*n*-C_4H_9	NH	1.5	71
2	*n*-C_5H_{11}	NH	1.5	75
3	Ph	NH	1.5	85
4	4-ClC_6H_4	NH	1.5	72
5	*c*-C_6H_{11}	NH	1.5	55
6	$Ph(CH_2)_2$	NH	1.5	60
7	Ph	O	3	83
8	*n*-C_4H_9	O	3	81
9	*n*-C_5H_{11}	O	3	82
10	$Ph(CH_2)_2$	O	3	75
11	4-CNC_6H_4	O	3	72
12	3-$MeOC_6H_4$	O	3	72

the 7-chloro-6-fluoro quinolone derivative can also be reacted under microwave irradiation with thiadiazole or oxadiazole-2-thiols to introduce this substituent in the 7-position of the ring.[725]

The saturated quinolone regioisomers, 4-hydroxyquinolinones, can be obtained by reaction of aniline derivatives with malonic ester derivatives in a microwave apparatus. For this procedure, the use of anilines with electron-donating substituents is advised, and the reaction should be performed in an open vessel in order to allow the alcohol formed during the condensation reaction to escape.[726]

With microwave irradiation, 2-aminochalcones can be cyclized to afford 2-aryl-tetrahydroquinolones in good to excellent yields (62−88%) (Scheme 172). For this reaction, montmorillonite clay[727] or silica gel impregnated with Lewis acid indium(III) chloride[728] should be used as inorganic support. Under conventional heating (140−150 °C), this reaction was observed to occur in good yields (70−92%) when silica gel supported $TaBr_5$ was used.[729] Recently, alumina-supported KF and alumina-supported

Scheme 171



Scheme 172

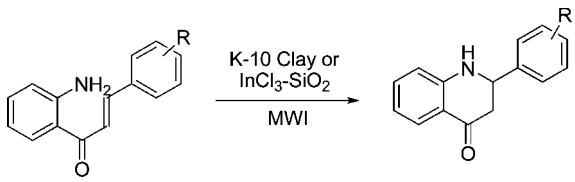
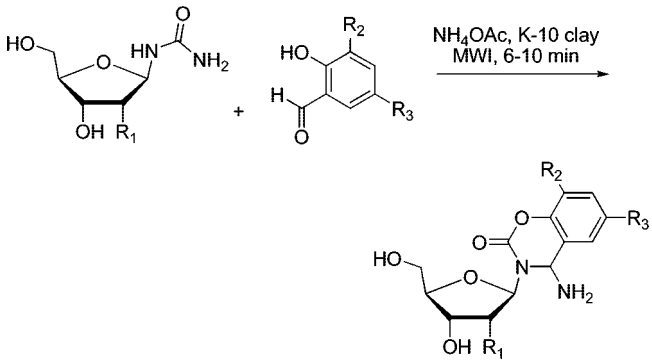


Table 107



entry	R_1	R_2	R_3	reaction time (min)	yield (%)
1	OH	H	H	8	71
2	OH	H	Br	10	80
3	OH	H	Cl	6	77
4	OH	OMe	H	8	73
5	OH	H	NO_2	6	75
6	H	H	H	8	68
7	H	H	Br	8	72
8	H	H	Cl	10	74
9	H	OMe	H	8	69
10	H	H	NO_2	10	76

$CeCl_3 \cdot 7H_2O-NaI$ were reported to be better catalysts since the reaction temperature can be lowered from 150 to 70 °C.[730]

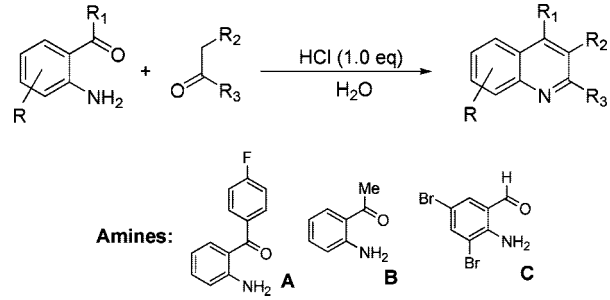
After the microwave-catalyzed Friedländer condensation was reported,[699] Wang et al. observed that through the use of higher power (450 W instead of the previous 300 W), 2-quinolones were preferentially formed under the reaction conditions. Cerium chloride heptahydrate was observed to be the best catalyst for this transformation resulting in the formation of 2-quinolones in excellent yields (85−91%) starting from several types of esters such as β-ketoesters, ethyl cyanoacetate, and diethyl malonate.[731]

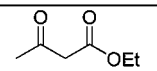
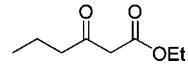
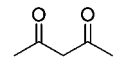
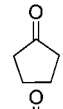
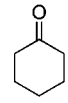
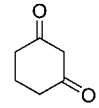
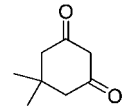
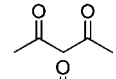
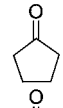
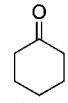
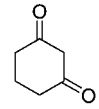
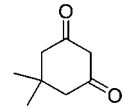
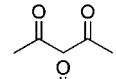
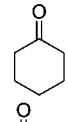
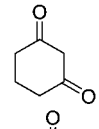
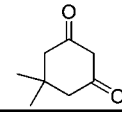
After the observation that montmorillonite K-10 clay was an efficient inorganic support for the three component reaction of substituted salicylaldehydes, N-substituted ureas or carbamates, and ammonium acetate,[732] 4-aminobenzoxazinone N-nucleosides were prepared following a facile procedure that consisted of the microwave irradiation of a mixture of ribosyl or deoxyribosylureas and salicylaldehydes with ammonium acetate in the presence of montmorillonite K-10 clay (Table 107). The authors claimed that the efficiency of the microwave irradiation should arise from the formation of a dipolar activated complex, since under conventional heating conditions the yields are much lower.[733]

7.1.2. Reactions in Aqueous Media

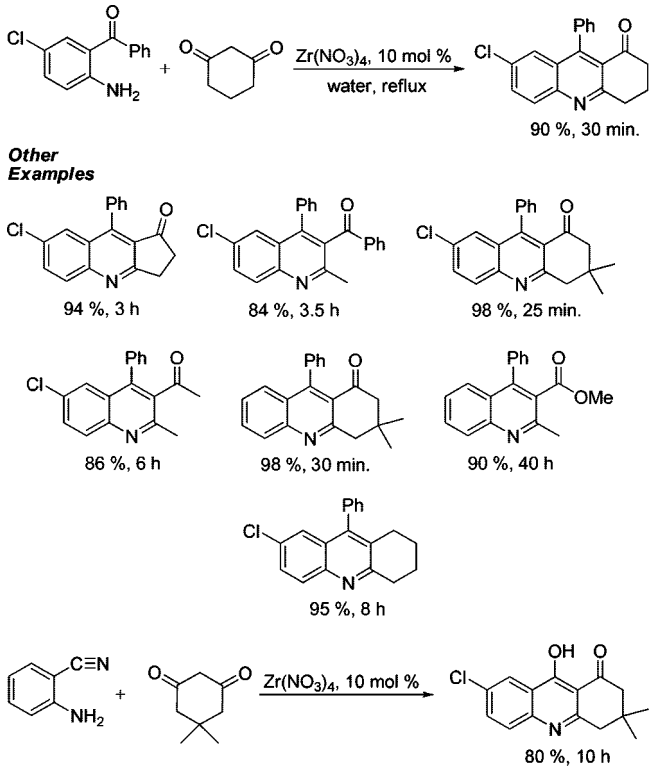
Quinolines are another important heterocyclic unit with wide occurrence in natural product structures. Wang et al. reported in a recent work the synthesis of substituted quinolines in water. This method relies on a simple Friedländer reaction of 2-aminoarylketones or 2-aminoarylaldehydes with carbonyl compounds in the presence of hydrochloric acid. As shown in Table 108, this method proved to be highly efficient to synthesize a variety of quinoline structures.[734]

Table 108



Entry	Ketone	Amine	Conditions	Yield (%)
1		A	60°C, 0.5 h	96
2		A	60°C, 1.5 h	92
3		A	60°C, 0.5 h	94
4		A	60°C, 1.0 h	91
5		A	60°C, 1.0 h	91
6		A	60°C, 0.5 h	93
7		A	60°C, 0.5 h	95
8		B	60°C, 1.0 h	92
9		B	60°C, 5.0 h	85
10		B	90°C, 2.0 h	92
11		B	60°C, 0.5 h	94
12		B	60°C, 0.5 h	95
13		C	90°C, 1.5 h	92
14		C	90°C, 6.0 h	90
15		C	90°C, 2.0 h	94
16		C	90°C, 2.0 h	95

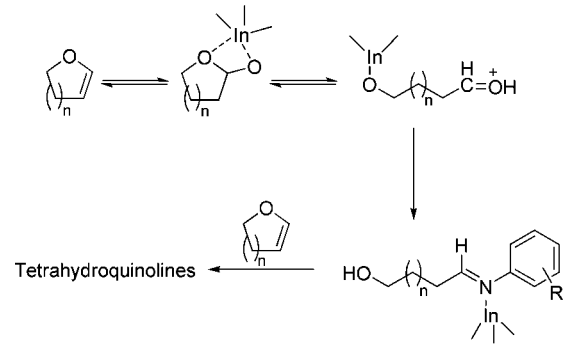
Scheme 173



The Friedländer reaction is still one of the most popular methods to prepare quinolines and involves the condensation of *o*-amino benzophenone with ketones or β-diketones. Zolfigol et al. recently disclosed the preparation of quinolines in water via the Friedländer annulation catalyzed by $Zr(NO_3)_4$ (or the Lewis acid $Zr(HSO_4)_4$ was shown to be also quite effective) (Scheme 173).[735,736] The annulation reaction was also accomplished using *o*-amino benzonitrile and dimedone affording hydroxyquinoline in good yields.

1,2,3,4-Tetrahydroquinoline moiety is rather important because it is present in various natural products. Furthermore many 1,2,3,4-tetrahydroquinolines display a broad range of biologically activity. With the goal of synthesising this important class of heterocycles, Li et al. studied the $InCl_3$-catalyzed domino reaction of aromatic amines with cyclic enol ethers in water. This system proved to be a highly efficient method to prepare 1,2,3,4-tetrahydroquinoline derivatives.[737,738] This transformation afforded the desired products in moderate to high yields with a general preference for the *cis* stereoselectivity (Table 109).[738] A tentative mechanism for the $InCl_3$-catalyzed tetrahydroquinoline synthesis in water was proposed and is presented in the Scheme 174.[738]

Scheme 174



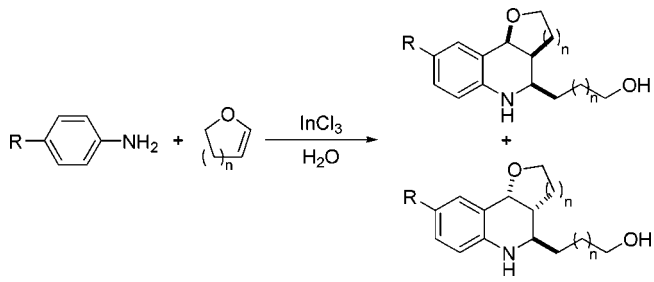
In subsequent work, Li et al. extended this methodology using a domino reaction of aromatic amines with cyclic hemiacetals. This fact constitutes an advantage over the method previously reported because it eliminates the use of limited availability cyclic enol ethers, Table 110.[739]

The synthesis of these important molecules was achieved in water without the use of a metal catalyst. Li et al. reported the domino reaction of aromatic amines with cyclic enol ethers over cation exchange resin ($H^{\oplus}$ form) catalyst in water, Table 111.[740]

A similar method was developed by Yadav et al. to prepare chiral tetrahydroquinolines. D-Glycals rapidly undergo cyclization in water with aryl amines in the presence of an equimolar amount of $CeCl_3 \cdot 7H_2O-NaI$ at 80 °C. This method afforded the desired tetrahydroquinolines in good yields and high stereoselectivities, Table 112.[741]

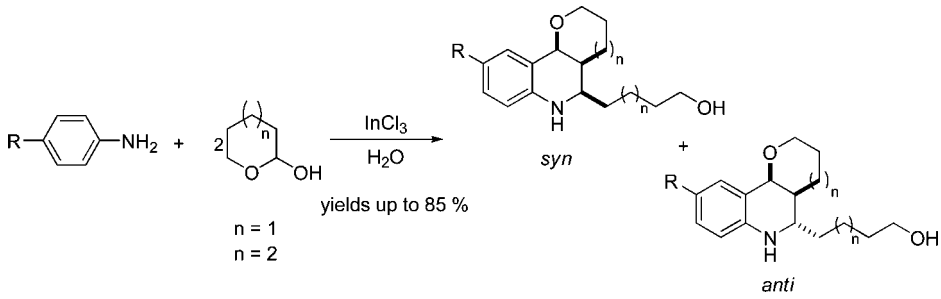
The Pictet−Spengler reaction can be performed in aqueous media and provides a useful method to prepare tetrahy-

Table 109



		$n = 1$		$n = 2$	
entry	R	conditions	yield (%) (*syn*/*anti*)	conditions	yield (%) (*syn*/*anti*)
1	H	50 °C, 10 h	85 (62/38)	rt, 48 h	85 (78/22)
2	CH_3	50 °C, 10 h	88 (57/43)	rt, 4 h	84 (81/19)
3	H_3CO	50 °C, 10 h	62 (66/34)	rt, 4 h	81 (87/13)
4	Cl	50 °C, 48 h	51 (57/43)	45 °C, 10 h	77 (74/26)
5	Br	50 °C, 48 h	36 (49/51)	45 °C, 10 h	81 (87/13)
6	F	50 °C, 4 h	68 (68/32)	rt, 10 h	81 (86/14)
7	HO	50 °C, 10 h	74 (74/26)	rt, 2 h	73 (96/4)
8	PhHN	rt, 10 h	87 (47/53)	rt, 10 h	65 (86/14)
9	NC	50 °C, 48 h	30 (34/66)	rt, 24 h	46 (69/31)

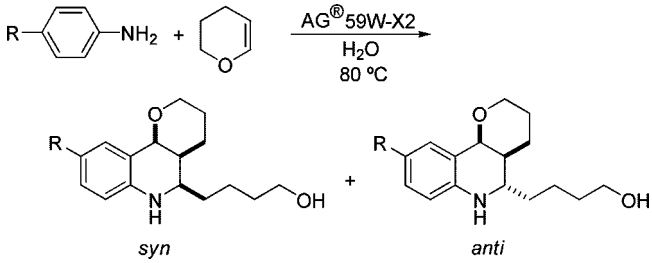
Table 110



entry	R	hemiacetal (*n*)	conditions	*syn*/*anti*	yield (%)
1	H	1	rt, 24 h	32/68	63
2	CH_3	1	50 °C, 12 h	43/57	85
3	H_3CO	1	50 °C, 12 h	47/53	61
4	Cl	1	50 °C, 12 h	45/55	47
5	Br	1	50 °C, 12 h	31/69	46
6	F	1	rt, 24 h	19/81	57
7	CN	1	50 °C, 24 h		*a*
8	H	2	rt, 48 h	46/54	76
9	CH_3	2	rt, 12 h	48/52	66
10	H_3CO	2	50 °C, 12 h	42/58	71
11	Cl	2	50 °C, 12 h	50/50	61
12	Br	2	50 °C, 12 h	39/61	44
13	F	2	rt, 24 h	52/47	66
14	NC	2	50 °C, 48 h	37/62	28

[a] Traces.

Table 111

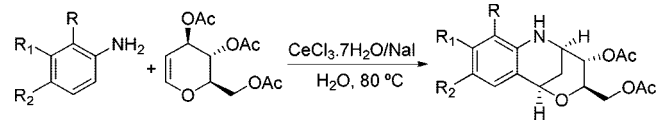


entry	R	conditions	*syn*/*anti*	yield (%)
1	H	80 °C, 2 h	47/53	77
2	H_3CO	80 °C, 4 h	47/53	69
3	CH_3	80 °C, 1.5 h	55/45	79
4	Cl	80 °C, 1 h	51/49	72
5	Br	80 °C, 2 h	44/56	59
6	F	80 °C, 1.5 h	58/42	68
7	NC	80 °C, 7 h	34/66	69

droisoquinolines. This reaction involves the cyclization of imines or iminium ions formed by the dehydration reaction of β-arylethylamine derivatives with aldehydes. Recently Saito et al. reported the perfluorooctanesulfonic acid (PFOSA)-catalyzed Pictet−Spengler reaction, which was conveniently accelerated by the addition of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP). This methodology allowed the preparation of these important heterocycles in good to excellent yields (Table 113).[742,743]

The same Pictet−Spengler reaction was used by Kundu et al. to prepare tetrahydro-β-carbolines in water. The heterocycles were obtained in moderate to good yields after the condensation of tryptophan, tryptamine, and *N*-benzyl tryptophan with several aldehydes in the presence of catalytic amounts of trifluoroacetic acid (TFA). An interesting aspect of this protocol is the fact that aryl aldehydes bearing electron-withdrawing or -donating groups underwent Pictet−Spengler reaction equally well (Table 114).[744]

Table 112



entry	R	conditions (h)	yield (%)
1	$R = R_1 = R_2 = H$	7.0	82
2	$R = R_1 = HR_2 = Cl$	8.0	80
3	$R = R_1 = HR_2 = Me$	7.5	85
4	$R = R_1 = HR_2 = F$	9.0	75
5	$R = R_1 = HR_2 = Br$	8.5	72
6	$R = R_2 = HR_1 = Me$	7.5	83
7	$R = R_1 = R_2 = OMe$	8.0	70
8	$R = R_2 = HR_1 = Cl$	9.0	80
9	$R = Cl; R_1 = Me; R_2 = H$	8.5	79
10	$R = Cl; R_1 = R_2 = H$	7.5	82
11	$R = Me; R_1 = R_2 = H$	8.0	86
12	$R = Br; R_1 = HR_2 = Me$	9.5	65
13	α-naphtalamine	8.5	70
14	2,6-dichloroaniline	8.0	*a*

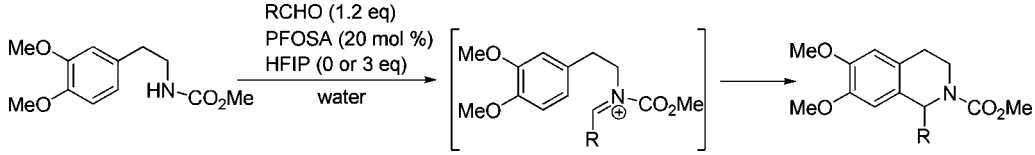
[a] No reaction.

7.1.3. Reactions in PEG or PEG Tag Approaches

The aza-Diels−Alder reaction between aromatic imines and olefins offers a method to obtain precursors of an important class of pharmacological compounds, quinolines. Wang et al. attached 4-formyl benzoic acid to a soluble polymer, PEG (MW = 3400), in a one-pot three-component reaction allowing preparation of several supported tetrahydroquinolines (Scheme 175). This protocol furnishes the desired precursors in high yields and purity by precipitation and methanolysis. Pyranoquinolines and furanoquinolines were synthesized from the related supported tetrahydroquinolines by oxidation with DQQ.[745]

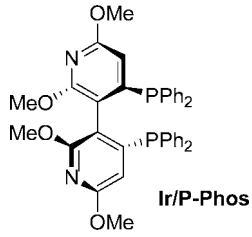
While looking for an air-stable iridium catalyst, Xu et al. found that Ir/P-Phos possesses those characteristics.[746] This catalyst could be prepared *in situ* by joining $[Ir(cod)Cl]_2$, (*R*)-P-Phos ligand, and iodide in THF and used to quantitatively hydrogenate quinolines in high enantioselectivities

Table 113



entry	aldehyde	HFIP (equiv)	conditions	yield (%)
1	$CH_3(CH_2)_5CHO$	3	4 h, rt	97
2	$CH_3(CH_2)_5CHO$		18 h, rt	84
3	$CH_3(CH_2)_{10}CHO$	3	4 h, rt	90
4	$CH_3(CH_2)_{10}CHO$		18 h, 60 °C	92
5	EtCHO	3	10 h, rt	95
6	EtCHO		5 h, 60 °C	99
7	formaline	3	8 h- rt	86
8	formaline		2 h, 60 °C	93
9	PhCHO	3	19 h, 90 °C	94
10	PhCHO		18 h, 90 °C	81
11	*i*-PrCHO	3	20 h, 90 °C	96
12	CyCHO	3	4 h, 90 °C	99
13	*t*-BuCHO	3	18 h, 90 °C	

(90−92% ee). After this success, the authors made some efforts to develop a protocol where the catalyst could be recycled. The first choices were immobilization on PEG (MW = 400 Da) and in ionic liquids. The catalytic system proved to be much less efficient in those solvents, and this was attributed by the authors to their high polarity. An alternative approach was found by the authors by using the less polar poly(ethylene glycol) dimethyl ether (DMPEG), in which the reaction was carried out with the same levels of efficiency, especially in a biphasic mixture with hexane. After the reaction was completed the hexane phase could be separated and the DMPEG phase was reused efficiently after further washings with hexane. The immobilized catalyst was reused 7 times without any negative impact on the reaction yield and selectivity. This method was lately expanded to other ligands such as chiral diphosphite H8-BINAPO ligands.[747]



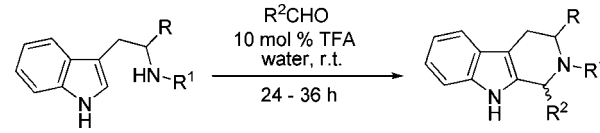
Ir/P-Phos

Schotten et al. prepared a library of biaryl 1*H*-benzimidazoles, 1*H*-imidazo[4,5-*b*]pyridines and 1*H*-imidazo[4,5-*c*]pyridines starting from the respective diamines and PEG-supported bisaryl-aldehydes in moderate yields using soluble polymer strategy (Scheme 176).[748]

7.1.4. Reactions in Ionic Liquids

The Friedländer reaction is an acid- or base-catalyzed condensation followed by a cyclodehydration between an aromatic 2-aminoaldehyde or ketone and a carbonyl compound containing reactive α-methlyene groups.[749,750] Recently, Wang et al.[751] reported a novel preparation of 4-phenylquinoline derivatives through acid-catalyzed Friedländer reaction in IL [bmim][BF_4] as solvent and sulfuric acid as catalyst (Table 115). This new methodology allowed higher yields than when a conventional solvent (glacial acetic acid) was used combined with the simplicity of the catalytic reaction media recovery and reuse. The catalyst and IL could

Table 114



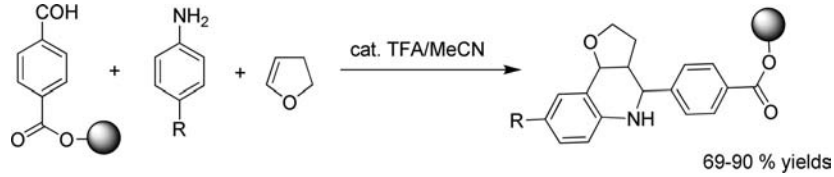
entry	R	R^1	R^2	yield (%)	*cis*/*trans*
1	CO_2CH_3	H	4-NO_2-C_6H_4	83	75:25
2	CO_2CH_3	H	C_6H_5	82	70:30
3	CO_2CH_3	H	4-CH_3-C_6H_4	75	83:17
4	CO_2CH_3	H	4-OH-C_6H_4	68	90:10
5	CO_2CH_3	H	4-$(CH_3)_2$N-C_6H_4	72	60:40
6	CO_2CH_3	H	4-Br-C_6H_4	77	80:20
7	CO_2CH_3	H	4-CH_3O-C_6H_4	79	55:45
8	CO_2CH_3	H	CH_3CH_2	65	70:30
9	CO_2CH_3	H	$C_6H_5CH_2$	68	75:25
10	H	H	4-NO_2-C_6H_4	72	
11	H	H	C_6H_5	75	
12	H	H	4-CH_3-C_6H_4	64	
13	H	H	2-OH-C_6H_4	61	
14	H	H	4-$(CH_3)_2$N-C_6H_4	45	
15	CO_2CH_3	$CH_2C_6H_5$	4-NO_2-C_6H_4	73	0:100
16	CO_2CH_3	$CH_2C_6H_5$	C_6H_5	77	0:100
17	CO_2CH_3	$CH_2C_6H_5$	4-CH_3O-C_6H_4	61	0:100

be recovered easily by drying at 80 °C under reduced pressure for several hours after the extraction of the product with diethyl ether.

Dabiri and co-workers have recently reported a one-pot combination of a modified Friedländer annulation and a Knoevenagel condensation to prepare 2-styrylquinolines in the presence of 1-methylimidazolium trifluoroacetate. The desired products were obtained in good to excellent yields (78−87%) after 2 h at 80 °C, before and after aldehyde addition.[752]

Pyranoquinoline derivatives are found to posses a wide range of biological activities such as anti-allergenic, anti-inflammatory, psychotropic, and estrogenic activity.[753,754] Normally, the imino-Diels−Alder provides easy access to the synthesis of pyrano- and furanoquinolines.[755,756] In this context, a novel synthetic method of three-component-coupling reactions of aldehydes, amines and cyclic enol ethers such as 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran under mild and convenient conditions was developed to afford the corresponding pyrano- and furanquinolines in excellent yields with high endo-selectivity using ILs as promoters (Table 116).[757,758] In the case of 2,3-dihydrofuran,

Scheme 175



Scheme 176

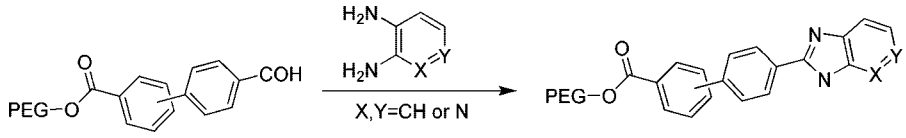
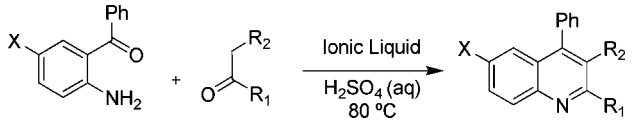


Table 115



entry	X	R_1	R_2	time (h)	yield (%)
1	H	C_6H_5	H	5	77 (1st cycle) 78 (2nd cycle) 75 (3rd cycle) 70 (4th cycle)
2	H	4-BrC_6H_4	H	5	82
3	H	4-$NO_2C_6H_4$	H	4	86
4	H	CH_3	H	8	72
5	Cl	C_6H_5	H	5	75
6	Cl	4-$CH_3C_6H_4$	H	5	72
7	Cl	4-ClC_6H_4	H	5	78
8	Cl	4-BrC_6H_4	H	5	80
9	Cl	4-$NO_2C_6H_4$	H	4	88
10	Cl	CH_3	H	8	73

this method afforded selectively endo-products under similar reaction conditions. The use of ILs as promoters for this transformation allows simple product isolation, use of moisture sensitive materials, avoidance of heavy metal Lewis acid procedures, and an easy reuse of this IL reaction media.

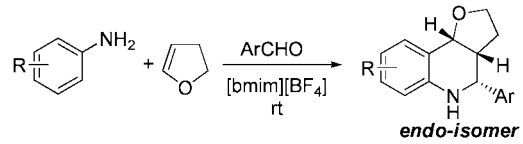
Several aldimines (formed *in situ* from aromatic aldehydes and anilines in ILs) reacted with 2,3-dihydrofuran in IL [bmim][BF_4] to afford the corresponding furano[3,2-*c*]quinines in high yields (85−92%). In all cases, the products were obtained exclusively as endo isomers, whereas under conventional conditions, the products were obtained as a mixture of endo and exo isomers favoring the endo diastereomer.[759] However, in the case of reaction of 3,4-dihydro-2*H*-pyran with imines in the presence of IL [bmim][BF_4], the product pyrano[3,2-*c*]quinolines were obtained as a mixture of endo and exo isomers, favoring endo diastereomers. In the absence of ILs, the reaction did not afford any product even after a long reaction time (15−20 h).

In the same line, Yadav et al.[760] described a method for the synthesis of tetrahydroisoquinolonic acids involving three-component-coupling reactions of aldehydes, amines, and homophthalic anhydride using ILs as solvent reaction media as well as promoters. Particularly relevant in this methodology are the improved yields, cleaner reaction profiles, enhanced rates, ease of recovery and reuse of the IL media, and greater *cis* selectivity, which make it an efficient and simple procedure to prepare isoquinoline derivatives of biological relevance.[754,761]

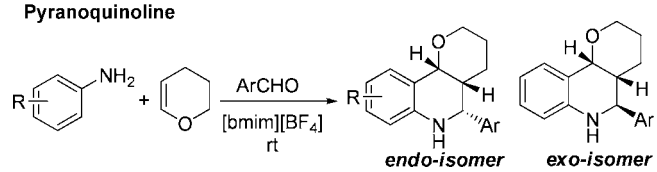
Initially, the authors tested the reaction of benzaldehyde, aniline, and homophthalic anhydride in IL [bmim][BF_4] at room temperature, which afforded the corresponding *cis*-isoquinolonic acid derivative in 90% yield. Then, several aldehydes and amines reacted efficiently with homophthalic

Table 116

Furanoquinolines

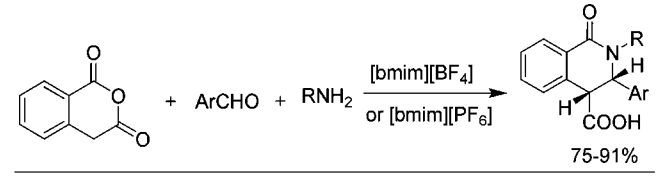


Pyranoquinoline



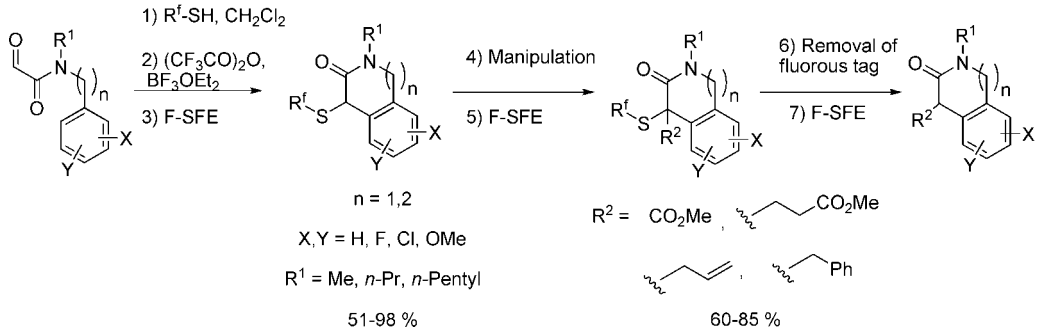
entry	R	Ar	enolether	time (h)	yield (%)	*endo*/*exo*
1	H	C_8H_5	DHF	3.5	92	
2	4-MeO	H	DHF	3.0	90	
3	H	4-FC_8H_4	DHF	3.5	89	
4	4-Me	4-ClC_6H_4	DHF	3.0	92	
5	H	4-$MeOC_6H_4$	DHF	2.5	90	
6	4-MeO	4-FC_8H_4	DHF	4.0	87	
7	3,5-$(MeO)_2$	4-FC_8H_4	DHF	3.5	85	
8	H	C_8H_5	DHP	3.0	91	90:10
9	H	4-FC_8H_4	DHP	3.5	89	85:15
10	2-Me	C_8H_5	DHP	2.5	90	80:20
11	4-MeO	C_8H_5	DHP	3.0	87	87:13
12	4-F	C_6H_5	DHP	3.5	89	85:15
13	1-napthyl	C_6H_5	DHP	4.0	85	80:20
14	1-napthyl	4-FC_8H_4	DHP	4.5	80	75:25

Table 117

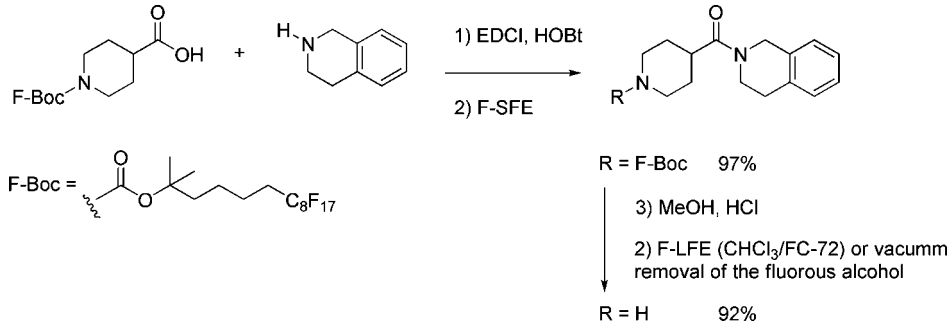


			5% $InCl_3$-[bmim][BF_4]		5% $InCl_3$-[bmim][PF_6]	
entry	X-$ArNH_2$(X)	Y-ArCHO (Y)	time (h)	yield (%)	time (h)	yield (%)
1	H	4-MeO	1.0	92	2.0	81
2	4-Me	H	1.0	90	1.5	85
3	H	H	0.5	95	1.0	87
4	4-Cl	2-Me	1.5	91	2.0	83
5	4-Br	H	1.0	89	2.5	80
6	4-MeO	2-Me	1.5	92	2.0	82
7	H	4-$N(Me)_2$	2.5	87	3.5	75
8	3,4,5-$(MeO)_3$	H	2.0	89	3.0	78
9	4-Me	4-MeO	1.5	91	2.5	82

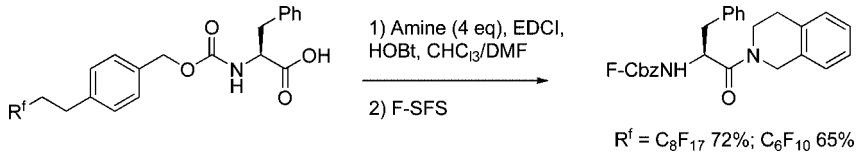
Scheme 177



Scheme 178



Scheme 179



anhydride to give the corresponding isoquinolonic acids in 75−91% of yield using ILs [bmim][BF_4] or [bmim][PF_6] (Table 117). This reaction was not successful in other ILs such as [bmim][Cl] or *n*-tetrabutyl ammonium chloride, [TBA][Cl]. The authors also performed this three-component coupling reaction using indium trichloride as catalyst in IL as well as in dichloromethane (DCM) to compare the efficiency of ILs tested.[760] These cyclization reactions proceeded smoothly in the presence of 5 mol % $InCl_3$ in both solvents, but the recovery and reuse of $InCl_3$ is very efficient and simple using IL media.

Polyhydroacridine derivatives can also be prepared by the three-component reaction of aldehydes, amines, and dimedone in ionic liquids. 1-*n*-Butyl-3-methylimidazolium bromide was used as solvent in the preparation of these tricyclic compounds.[762]

7.1.5. Reactions in Fluorinated Fluids

Procter et al. used 1*H*,1*H*,2*H*,2*H*-perfluoro-decanethiol for the synthesis of several oxindoles, tetrahydroisoquinolinones, and tetrahydrobenzazepinones by Pummerer cyclization. The thioether functional group was further used for chemical manipulation such as Michael addition or alkylation. The fluorous tag was removed by oxidation to the corresponding sulfone followed by SmI_2 treatment[763] or by oxidative cleavage using ceric(IV) ammonium nitrate (CAN).[764] The intermediates containing the fluorous tag and the products were purified by F-SFE (Scheme 177).

Protecting groups containing fluorous tags are extremely useful because apart from the desired protection function they also facilitate the purification process by F-SPE. Fluorous Boc (^{F}Boc) and Cbz have been widely used for nitrogen protection.[63] Curran et al. demonstrated the advantage of the use of these protecting groups in combination with F-SPE for representative reactions and for library synthesis.[765,766] Some illustrative examples are presented in Schemes 178 and 179.

The combination of F-SPE with molecules containing fluorous tags as protecting groups, scavengers, or anchoring groups is extremely useful for the synthesis of libraries of compounds.[767] For example, Curran et al. prepared a 560-membered library of analogues of the natural product mappicine by this approach **(**Scheme 180**)**.[768]

7.2. Containing Two Nitrogen Atoms

7.2.1. Solvent-Free Reactions

For the preparation of quinazoline derivatives, a simple and efficient method can be adopted by reacting *N*-arylamidines or guanidines with an aldehyde under solvent-free conditions (Table 118). This procedure can also be extended to the synthesis of benzo[*g*]quinazoline derivatives.[769] 4-Aminoquinazolines can be prepared in good yields (73−90%) in a microwave environment for a couple of minutes by reaction of cyanoaromatic compounds with anthranilonitrile in the presence of 10 mol % potassium *t*-butoxide.[770]

4-Aminoquinazoline derivatives can be prepared by the substitution of the chlorine atom by aliphatic amines in 5 min under MWI. When anilines are used, the product formation is strongly dependent on the aniline substituents,

Scheme 180

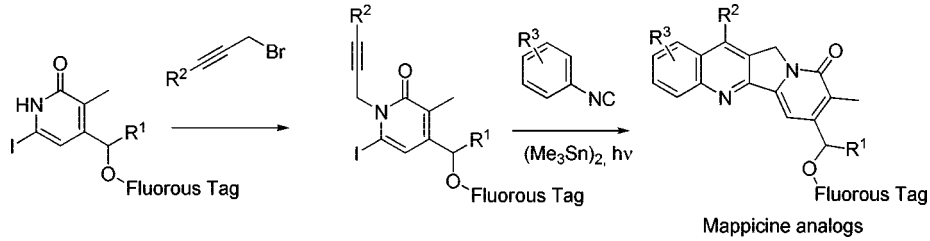
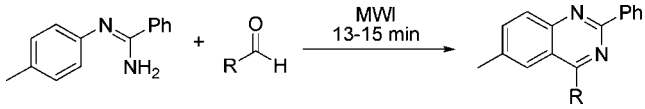
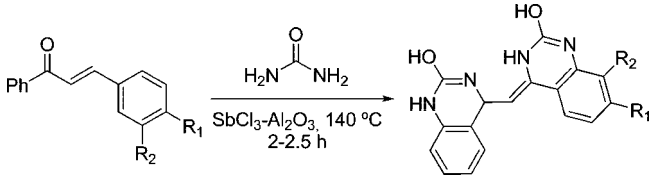


Table 118



entry	1	2	3	4	5
R	Ph	4- $NO_2C_6H_4$	4-$MeOC_6H_4$	4-$Me_2NC_6H_4$	4-ClC_6H_4
yield (%)	76	77	74	70	73

Table 119

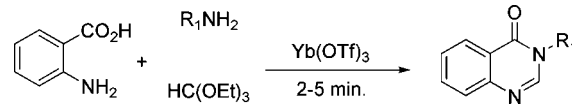


entry	R_1	R_2	yield (%)
1	H	H	82
2	Cl	Cl	85
3	OMe	H	82
4	F	H	80
5	Br	Br	81
6	Cl	H	85
7	OMe	OMe	80

and thus, longer reaction times are needed (10 min) to achieve the desired products in good to excellent yields (60−98%).[771] Using $SbCl_3-Al_2O_3$ as catalyst, 4*H*,4′-exomethylene-bis[quinazolin-2-enols] can be efficiently prepared through solvent-free reaction of benzylideneacetophenone with urea (2 equiv) at 140 °C (Table 119).[772]

For the preparation of quinazolin-4(3*H*)-ones there are several methods under solvent-free conditions, most of them based on the three-component cyclocondensation of anthranilic acid with amines and ortho esters. For instance, a completely solvent-free procedure can be efficiently used by employing lanthanide triflates, particularly ytterbium triflate, as catalysts for this cyclocondensation under conventional heating (60 or 80 °C). Excellent yields of the desired products can be obtained in a few minutes (2−5 min), particularly if electron-donating groups are present in the aniline (Table 120).[773] Similarly, Yb(III) supported on Amberlyst 15 resin (Yb-resin),[560] silica gel supported ferric chloride,[774] lanthanum(III) nitrate hexahydrate, and *p*-toluenesulfonic acid[775] were also reported as efficient catalysts for this reaction. In the microwave version of this reaction, Nafion-H was reported to be a suitable catalyst even when anthranilic anhydride was used.[776] The Niementowski reaction, consisting of the condensation of anthranilic acid with formamide, can also be performed under microwave irradiation.[777] Despite a high excess of formamide (5 equiv) that has to be used in order to improve the reaction yield, this procedure can also be efficiently applied for the synthesis of tetracyclic 8*H*-quinazolino[4,3-*b*]quinazolin-8-ones.[778] Recently, 3-substituted quinazolin-4(3*H*)-ones were also reported to be

Table 120



entry	R_1	yield (%)
1	Ph	99
2	2-MeC_6H_4	98
3	3-MeC_6H_4	95
4	4-MeC_6H_4	99
5	3,4-$Me_2C_6H_3$	99
6	4-EtC_6H_4	99
7	3-$MeOC_6H_4$	98
8	4-$MeOC_6H_4$	98
9	2-ClC_6H_4	97
10	3-ClC_6H_4	94
11	4-ClC_6H_4	95
12	4-FC_6H_4	94
13	2-$NO_2C_6H_4$	85
14	3-$NO_2C_6H_4$	82
15	4-$NO_2C_6H_4$	80
16	2,4-$(NO_2)_2C_6H_4$	75
17	4-$NHAcC_6H_4$	97
18	$PhCH_2$	96

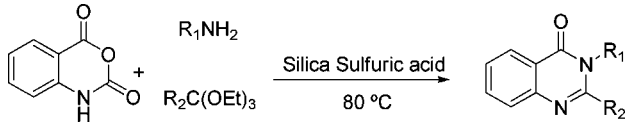
synthesized under MWI through this method forming the formamide *in situ* through the presence of formic acid and a primary amine.[779]

The employment of isatoic anhydride, instead of anthranilic acid, also leads to the formation of 2,3-disubstituted quinazolin-4(3*H*)-ones under conventional heating in presence of amines and orthoester derivatives using silica sulfuric acid as catalyst[780] (Table 121). Instead of silica sulfuric acid, diammonium hydrogen phosphate can be used as catalyst at the same temperature for 5−7 h.[181]

As a method to manipulate the N-3 substituent, ammonium acetate can be used under these reaction conditions[781] or by microwave-induced cyclocondensation of anthranilic acid without catalyst.[782] On the other hand, a mixture of $AlCl_3$/$ZnCl_2$ supported on silica gel is a good catalyst for the cyclocondensation of isatoic anhydride and 2-aminobenzamides by conventional heating conditions or through the employment of microwave irradiation,[783] while silica-supported sulfuric acid has been reported as a good catalyst for the microwave-induced condensation of 2-aminobenzamides with orthoester derivatives.[784] Furthermore, when microwave irradiation is employed in the absence of any catalyst, the use of formic acid in place of orthoester derivatives also leads to the formation of quinolinones.[785]

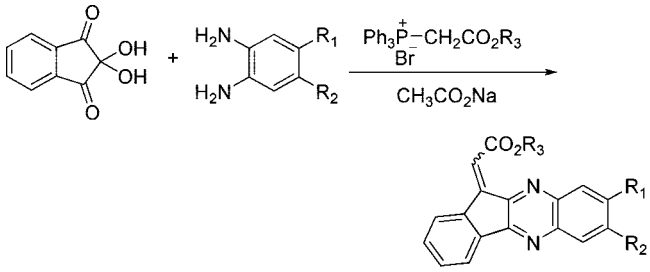
Another one-pot cyclocondensation procedure consisting of microwave irradiation of anthranilic acid, phenyl acetyl chloride, and fluorinated anilines has been described as a good method to obtain quinazolinone fluorinated derivatives.[786] Anthranilic acid can also be employed in the microwave-induced condensation with lactams in the absence of any catalyst. This procedure has been successfully applied to the synthesis of analogues of cytotoxic alkaloid luotonin A.[787]

Table 121



entry	R_1	R_2	yield (%)
1	4-ClC_6H_4	Me	78
2	4-MeC_6H_4	Me	80
3	Ph	Me	81
4	4-EtC_6H_4	Me	80
5	$PhCH_2$	Me	85
6	$PhCH_2CH_2$	Me	83
7	Et	Me	87
8	2-MeC_6H_4	Me	81
9	Et	Et	86
10	4-MeC_6H_4	Et	81
11	4-BrC_6H_4	Et	78
12	4-MeC_6H_4	*n*-Pr	84
13	$PhCH_2CH_2$	*n*-Pr	81
14	4-BrC_6H_4	*n*-Pr	77
15	Ph	*n*-Pr	80
16	4-MeC_6H_4	*n*-Pr	79
17	$PhCH_2CH_2$	*n*-Bu	79
18	Ph	Ph	79
19	4-MeC_6H_4	Ph	78
20	4-ClC_6H_4	Ph	75
21	$PhCH_2CH_2$	Ph	80

Table 122



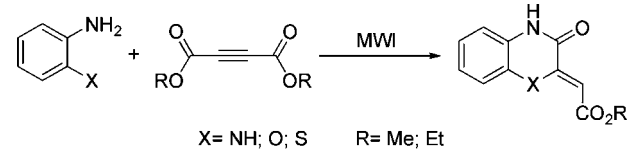
entry	R_1	R_2	R_3	reaction time (h)	yield (%)
1	H	H	Me	1.5	70
2	H	H	Et	1.5	77
3	Me	H	Me	1.5	76
4	Me	H	Et	1.5	89
5	Me	Me	Me	2	80
6	Me	Me	Et	2	75
7	H	NO_2	Me	1	93
8	H	CO_2H	Me	1	94

The synthesis of complex three-fused heterocycles containing a quinazoline ring system, pyrazino[2,1-*b*]quinazoline-3,6-diones, can be achieved through microwave irradiation of anthranilic acid and iminoethers.[788]

2,3-Disubstituted quinoxaline derivatives can be prepared through the microwave induced condensation of alkyl or aryl acyloins and *o*-phenylenediamine without the use of any inorganic support. Depending on the acyloin substituents, the yields may vary as already seen when benzoin is used, in which the saturated 2,3-diphenyl-1,2-dihydroquinoxaline was obtained as the major product.[789] Acidic alumina as inorganic support was recently reported to be a good catalyst for the benzil condensation with *o*-phenylenediamines.[790]

The one-pot three-component condensation of ninhydrin and phenylenediamine derivatives can be efficiently performed at room temperature in the presence of triphenylphosphonium bromide salts and sodium acetate. Through this method, alkyl indeno[1,2-*b*]quinoxalin-11-ylideneacetates can be obtained in reasonable to good yields (Table 122).[791]

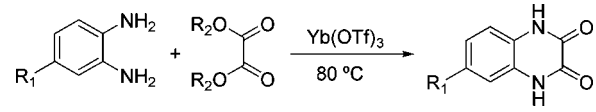
Scheme 181



Through the microwave-induced addition of dialkyl acetylenedicarboxylates to *o*-phenylenediamine, *o*-aminophenol, and *o*-aminothiophenol, the correspondent heterocycles can be obtained in good yields (75−96%) (Scheme 181).[792]

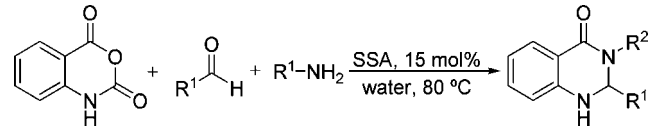
The Phillips-type heterocyclization of 1,2-phenylenediamines and alkyl oxalates to afford quinoxaline-2,3-diones is a good method for the preparation of such compounds. The use of ytterbium triflate as catalyst of this reaction leads to good yields of the desired heterocyles, in particular when no solvent is used (Table 123). Furthermore, the catalyst can be recovered and recycled after an aqueous work-up.[793] In

Table 123



entry	R_1	R_2	yield (%)
a	H	Et	89
b	H	*i*-Pr	81
c	H	*n*-Bu	87
d	Me	Et	82
e	NH_2	Et	79
f	Cl	Et	83
g	NO_2	Et	80

Table 124



entry	R^1	R^2	conditions (h)	yield (%)
1	Ph	H	3	84
2	4-ClC_6H_4	H	3	81
3	2-$CH_3OC_6H_4$	H	3	85
4	4-$CH_3C_6H_4$	H	3	86
5	Ph	Me	3	85
6	4-ClC_6H_4	Me	3	83
7	4-$CH_3OC_6H_4$	Me	3.5	86
8	4-$CH_3OC_6H_4$	Et	3	86
9	4-ClC_6H_4	Et	3.5	84
10	4-$NO_2C_6H_4$	Et	3	86
11	3-$NO_2C_6H_4$	Et	3.5	84
12	Ph	Et	3.5	86
13	4-$NO_2C_6H_4$	*n*-Pr	3.5	87
14	4-OHC_6H_4	Et	3.5	82
15	4-ClC_6H_4	*n*-Bu	3.5	89
16	Ph	Ph	4.5	85
17	4-$NO_2C_6H_4$	Ph	4.5	80
18	3-$NO_2C_6H_4$	Ph	5	79
19	Ph	4-ClC_6H_4	5	78
20	2-OH-4-ClC_6H_3	Ph	5	76
21	2-OH-4-ClC_6H_3	4-$CH_3OC_6H_4$	5.5	79
22	2-thiazolyl	4-ClC_6H_4	5.5	77
23	2-thiazolyl	4-$NO_2C_6H_4$	5.5	81
24	2-thiazolyl	4-OHC_6H_4	5.5	76
25	2-thiazolyl	4-$CH_3C_6H_4$	5.5	78
26	2-thiazolyl	4-$NO_2C_6H_4$	5	75

Scheme 182

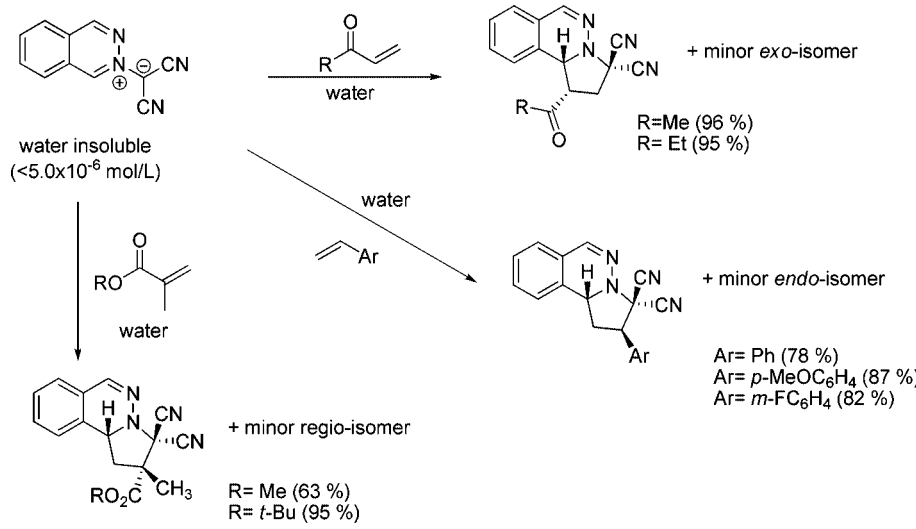
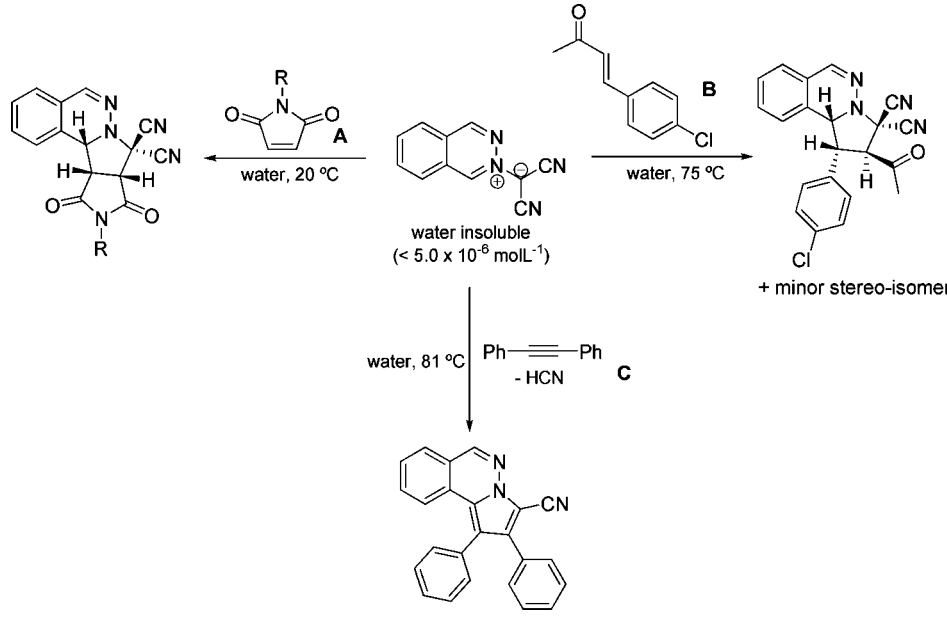


Table 125



entry	dipolarophile	mp (°C)	molar solubility (mol L^{-1})	conditions	yield (%)
1	**A**, R = *p*-$MeOC_6H_4$	130−132	2.2×10^{-2}	24 h, 20 °C	95
2	**A**, R = Ph	89−90	1.2×10^{-2}	24 h, 20 °C	96
3	**A**, R = CH_2Ph	70	3.2×10^{-3}	24 h, 20 °C	91
4	**A**, R = *p*-ClC_6H_4	95−97	2.0×10^{-3}	24 h, 20 °C	94
5	**A**, R = *p*-BrC_6H_4	128−130	1.7×10^{-3}	24 h, 20 °C	93
6	**A**, R = *p*-$NO_2C_6H_4$ MI	168−170	1.7×10^{-3}	24 h, 20 °C	95
7	**B**	58−62	1.2×10^{-4}	48 h, 20 °C	<1
8	**B**	58−62	1.2×10^{-4}	48 h, 20 °C	3.5
9	**B**	58−62	1.2×10^{-4}	24 h, 75 °C	86
10	**C**	59−61	1.8×10^{-5}	24 h, 20 °C	<1
11	**C**	59−61	1.8×10^{-5}	24 h, 81 °C	71

the case of the microwave-induced version for this condensation, *p*-TsOH can be used in the absence of any support.[794]

1,4-Dioxo-3,4-dihydrophthalazine-2(1*H*)-carboxamides or -carbothioamides can be synthesized from the reaction of different phthalic anhydrides with semicarbazide or thiosemicarbazide using montmorillonite KSF clay as heterogeneous catalyst under MWI.[795] If an excess of phthalic anhydride is used, phthalazino[2,3-*b*]phthalazine-5,7,12,14-tetraones can also be obtained.[796]

7.2.2. Reactions in Aqueous Media

2,3-Dihydroquinazolinones are an interesting class of heterocycles, which display an array of interesting pharmaceutical properties, namely, antibacterial, antitumor, antifungal activity, and monoamine oxidase inhibition. Recently Dabiri et al. disclosed the preparation of 2,3-dihydroquinazolin-4(1*H*)-ones in water. These heterocycles were prepared in water via reaction of isatoic anhydride, a primary amine,

Scheme 183

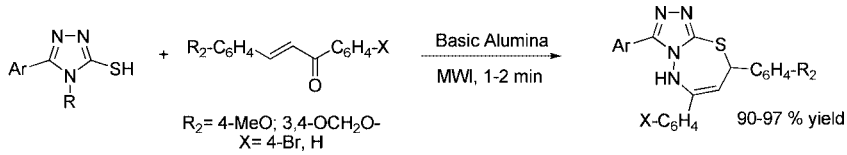
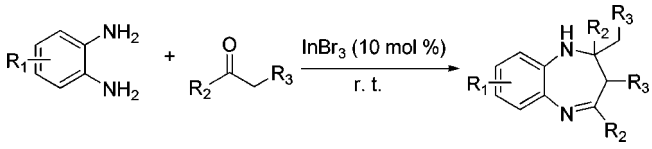


Table 126



entry	R_1	R_2	R_3	reaction time (h)	yield (%)
1	H	Me	H	1.5	95
2	H	Et	H	1.5	91
3	H	Et	Me	2.0	94
4	H	$CH_2CH(Me)_2$	H	2.5	87
5	4-Me	Me	H	1.5	96
6	4,5-Me_2	Me	H	1.5	97
7	4-Cl	Me	H	2.0	93
8	4-NO_2	Me	H	3.0	85

or ammonium acetate and an aromatic aldehyde catalyzed by silica sulfuric acid (SSA) (Table 124).[797]

Exploring the concept of "on water" reactions, Butler et al. suggested that when one or both reactants are liquids, the reactions could readily be occurring through an interfacial oily phase penetrated by water where both reactants are present at low concentrations. This oil phase was envisioned by the authors as a single-phase nanoemulsion created by the vigorous stirring when one of the reactants is a liquid. This concept was explored in 1,3-dipolar cycloadditions of water insoluble phthalazinium-2-dicyanomethanide and insoluble alkene and alkyne dipolarophiles.[798−800] These reactions afforded high yields of cycloadducts (Scheme 182). Then Butler et al. extended this study to a number of cases where both reactants were water-insoluble solids (Table 125). In this case, it was observed that in order to achieve high yields of cycloaddition products and when the solubility of both reactants are below the millimolar level, liquefaction of one is necessary in order to allow the reaction to pass through a water-penetrated oily phase.[801]

8. Seven-Membered Rings

8.1. Solvent-Free Reactions

Benzodiazepines are an important class of pharmacologically active compounds generally used as hypnotic, anti-anxiety, and anti-convulsant agents.[802]

The efficient indium(III) bromide has been used in a solvent-free synthesis of several highly valuable 1,5-benzodiazepine derivatives. By this procedure, *o*-phenylenediamines are reacted at room temperature with a ketone with at least one hydrogen atom in the α-position (Table 126). When cyclic ketones such as cyclopentanone, cyclohexanone, or cycloheptanone are used, the correspondent benzodiazepines can also be obtained in good yields (79−86%, not represented in the scheme). From testing of several Lewis acids, $InBr_3$ proved to be the most efficient catalyst for this reaction.[803] Recently, sulfamic acid was also reported as a catalyst for this reaction leading to better yields under solvent-free conditions than in solution.[804,805] When such condensation is carried under MWI, acetic acid can be used

Scheme 184

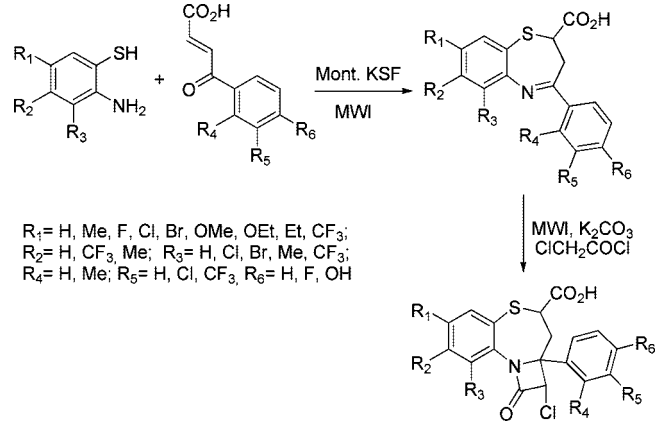
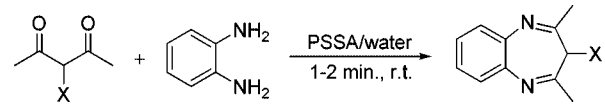


Table 127



entry	X	yield (%)
1	H	90
2	Cl	85
3	Me	86
4	Et	88

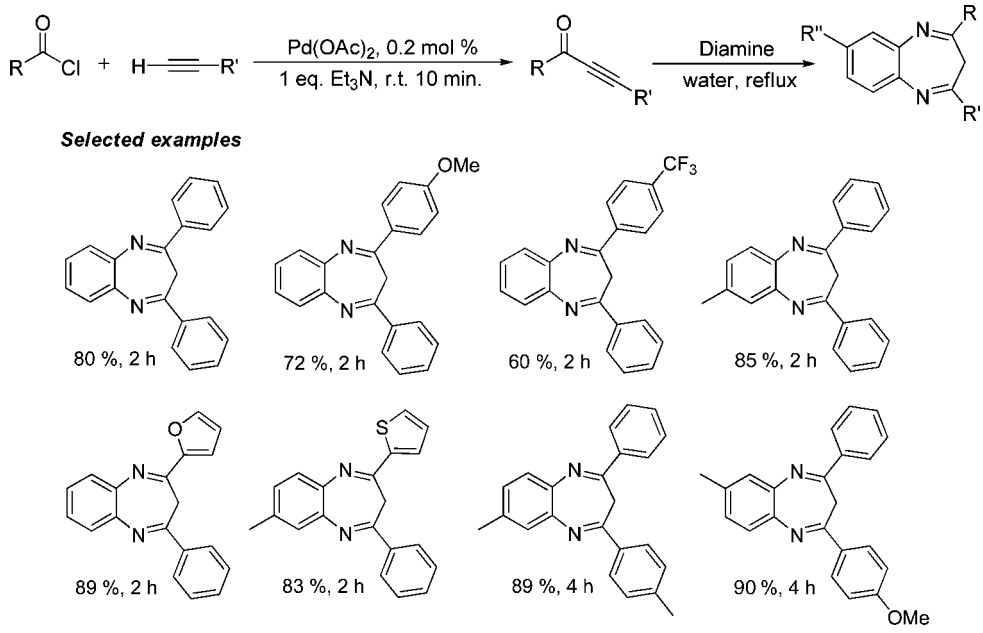
as catalyst, leading to the desired benzodiazepines in excellent yields (90−99%) in up to 7 min of reaction time.[806] In a room temperature procedure, the reaction of 2,2-dimethoxypropane with *o*-phenylenediamines in the presence of bismuth triflate yielded the 1,5-benzodiazepines after 2−4 h reaction time.[722]

Recently, an efficient procedure for the preparation of benzo[*b*]1,4-diazepines based on the use of $SbCl_3-Al_2O_3$ as catalyst was developed. These compounds were prepared in good yields (83−94%) through the catalyzed condensation of *o*-phenylenediamine and benzylidene acetophenones at 60 °C (up to 2 h of conventional heating) or through exposure to sun rays.[807]

For the preparation of biologically active thiadiazepines, a solvent-free procedure has been developed through the use of microwave irradiation. This procedure consists of reaction of 1-amino-2-mercapto-5-substituted triazoles and substituted chalcones using basic alumina as support (Scheme 183). It should be noted that when this reaction is performed in solution phase, using acetone as solvent and K_2CO_3 as base, longer reaction times are needed and the reaction product is obtained in lower yields.[808] Recently, *p*-TsOH was reported as a suitable catalyst for this transformation under microwave irradiation, while by the conventional heating method the yields were seen to be worse.[809]

Through the use of montmorillonite KSF together with microwave irradiation, 2-carboxy-2,3-dihydro-1,5-benzothiazepines can be prepared after reaction between substituted aminobenzenethiol and 3-(substituted benzoyl)-2-propionic acid (Scheme 184). This product can be further reacted with

Scheme 185



chloroacetyl chloride on potassium carbonate in order to form β-lactam fused benzothiazepine derivatives.[810]

8.2. Reactions in Aqueous Media

Similarly to the preparation of pyrazoles by condensation of hydrazines/hydrazides, polystyrene-supported sulfonic acid (PSSA) was also used as catalyst in the condensation of diamines with several 1,3-diketones to afford the desired benzodiazepines (Table 127). When a β-keto ester was used as the carbonyl compound, no reaction was observed.[400]

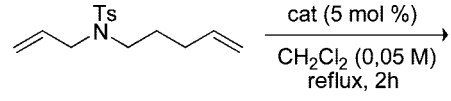
The preparation of diazepines in water was also accomplished by Srinivasan et al. using a one-pot three-component methodology. The protocol starts with ynone formation via palladium-catalyzed coupling of acid chlorides with terminal alkynes followed by Michael addition and cyclocondensation of *o*-phenylenediamines in water affording diazepines in moderate to good yields (Scheme 185).[811]

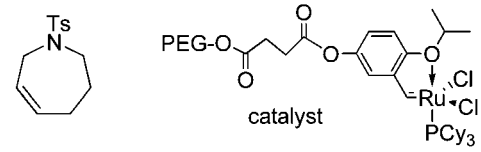
8.3. Reactions in PEG or PEG Tag Approaches

One of the most successful strategies for constructing large rings is ring-closing metathesis. Yao demonstrated that metathesis using a ruthenium catalyst could be performed by attaching the catalyst to a soluble polymer, like PEG_{5000}, via a succinic moiety and could be used efficiently to prepare tetrahydro-azepines.[217] The catalyst could be recovered by precipitation with diethyl ether at the end of the reaction and be reused with a similar degree of efficiency (Table 128).

Alternatively to ring-closing metathesis reactions, intramolecular Heck couplings constitute another reliable method for constructing cyclic molecules with a large number of atoms. Lamaty and co-workers prepared several

Table 128



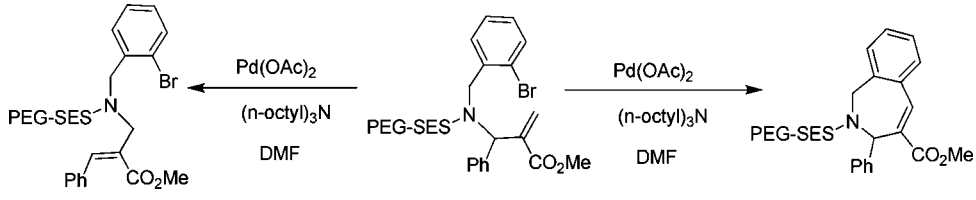


cycle	1	2	3	4	5	6	7	8
conversion (%)	98	97.5	96.5	95	95	93	93	92

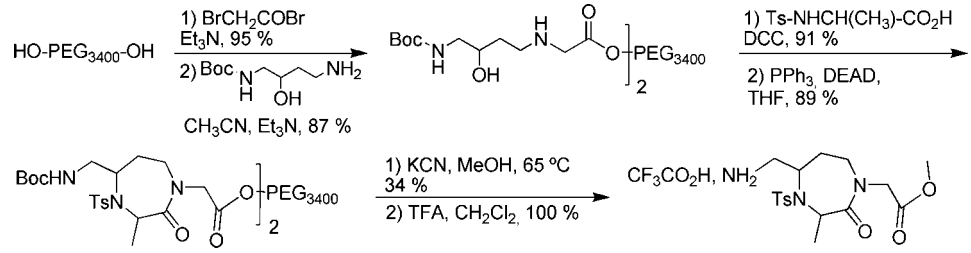
benzazepines supported on PEG_{3400} in good yields using this last type of cyclization (>79%).[812,813] Once again, precipitation with diethyl ether allowed an easy way to purify product. Interestingly, the large polymeric support stabilized the palladium catalyst through formation of nanoparticles. This stability allowed the reaction to run in the absence of phosphine ligands and ammonium salts with high selectivity toward Tsuji−Trost allylation (Scheme 186).

Perhydro-(1,4)-diazepinones are seven-membered rings with a conformational configuration similar to the γ-turn of peptides. Lazaro et al. showed that this heterocycle could generally be constructed starting from the acyclic precursor immobilized in a soluble polymer support (PEG, MW = 3400, Scheme 187). This strategy retained the same level of efficiency observed with unsupported precursors in the ring closure step (intramolecular Mitsunobu reaction). Furthermore, the byproduct formed during the cyclization (Ph_3PO) could efficiently be sepa-

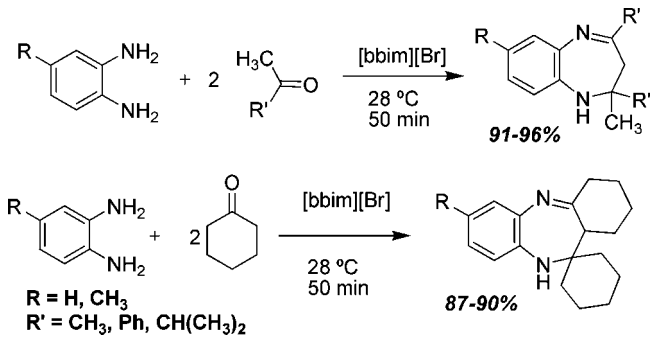
Scheme 186



Scheme 187



Scheme 188



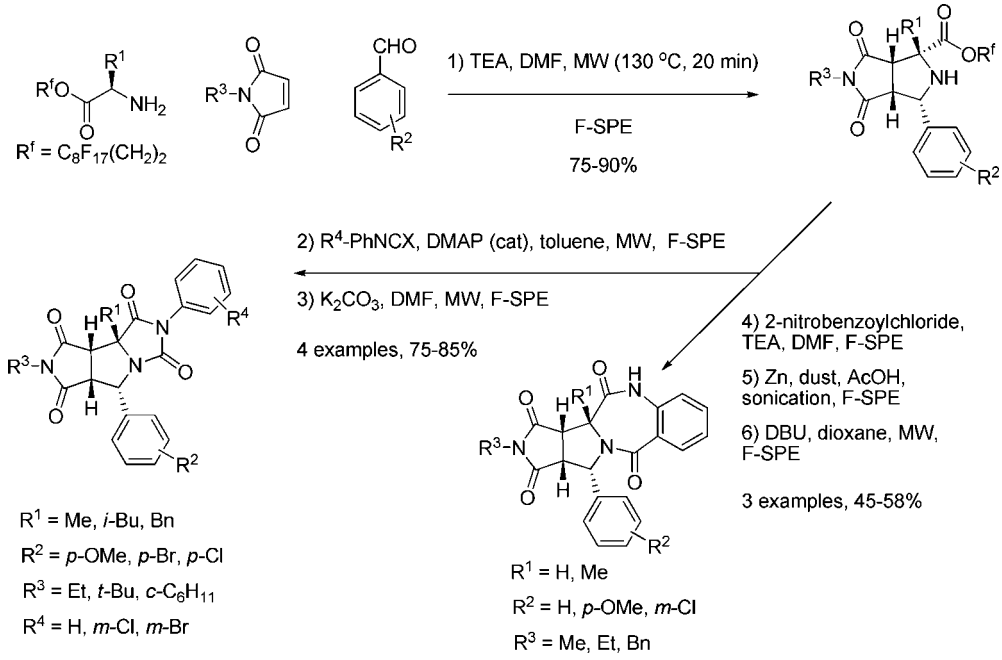
rated from the heterocycle more easily than with unsupported protocols.[814]

8.4. Reactions in Ionic Liquids

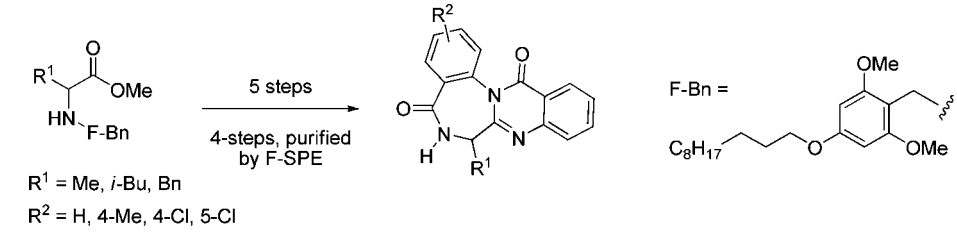
The reaction of *o*-phenylenediamines with both acyclic and cyclic ketones in IL [bbim][Br] afforded 1,5-benzodiazepines in good yields in the absence of a catalyst (Scheme 188).[815] The methods described in the literature for the synthesis of 1,5-benzodiazepines include condensation reactions of *o*-phenylenediamines with α,β-unsaturated carbonyl compounds,[816] β-haloketones,[817] or ketones in the presence of $NaBH_4$,[818] polyphosphoric acid or SiO_2,[819] BF_3-etherate,[820] $Yb(OTf)_3$,[821] Al_2O_3/P_2O_5, or AcOH under MW irradiation conditions.[806,822] Some of these processes showed limitations such as low to moderate yields, long reaction times, use of harsh conditions and expensive reagents, and observation of side reactions.

The alternative process using an IL not only as a solvating medium but also as a promoter for the reaction allowed significant advantages like use of mild conditions, easy work-up procedures, short reaction times, the absence of a catalyst, and efficient recyclability of IL media. The enhanced reactivity for the synthesis of the benzodiazepines in the imidazolium IL even in the absence of catalyst may be justified by the inherent Bronsted and Lewis acidities of the

Scheme 189



Scheme 190



ring hydrogens H2, H4, and H5 of the imidazolium cation in [bbim][Br].[823,824]

Beckmann rearrangement of ketoximes was reported to occur in a task-specific ionic liquid consisting sulfonyl chloride. The ε-caprolactam product was easily recovered from the reaction media with water extraction due the high solubility of the product in water and the low miscibility with the ionic liquid. Quantitative conversions and excellent selectivity were observed for the preparation of ε-caprolactam.[825] This compound can also be obtained from the depolymerization of nylon-6 under extremely high temperatures (around 300 °C) and employing quaternary ammonium salts as solvent. When higher temperatures were used, caprolactam derivatives with parts of the ionic liquid incorporated were obtained. The reutilization of the reaction media was tested for five cycles without significant decomposition.[826]

8.5. Reactions in Fluorinated Solvents

Starting from fluorous L-α-amino esters, the authors synthesized a range of tricyclic fused hydantoins and piperezinediones, as well two libraries of compounds, by performing several transformations under microwave irradiation (MW) and purification by F-SPE, including the key step of a one-pot, three-component [3 + 2] cycloaddition of azomethine ylides (Scheme 189). The fluorous tag was removed during the last cyclization promoted by base (K_2CO_3 and DBU).[827,828]

Zhang et al. described a multistep synthesis of nine benzodiazepine-quinazolines derived from fluorous benzyl protecting α-amino acid methyl esters in which the F-SPE procedure was used in the purification process of each step (Scheme 190).[829]

9. Conclusions

The development of more environmentally friendly methodologies is certainly a very current topic, which covers the synthesis of a wide range of molecules. As expected, N-based heterocycles has been the object of considerable focus during the last years. From the combined overview provide in this review, it can be seen that many well-established different methodologies were successfully applied by world wide laboratories to more environmentally benign approaches, such as reacting without solvent, using more readily reusable reaction media, such as water, ionic liquids, fluorinated solvents, or $scCO_2$, or attaching the catalyst or some substrate intermediate to a support, such as PEG or a fluorous tag, that facilitates the separation process. Additionally, in many reported approaches, improvement not only of the overall separation process but also of the reaction performance, such as higher yields, regio- or stereoselectivities, as well of the use of milder conditions was described. On the other hand, some, although to a lesser extent, new synthetic approaches were developed for the specific aim of achieving a more sustainable transformation. At the current state of the art, it is expected that more developments will emerge not only in line with the previous ones reported but also in the following more fascinating specific areas: (i) asymmetric and non-asymmetric bio- and organocatalysis; (ii) efficient organometallic catalysis with minimal contamination of toxic metals; (iii) more efficient or new one-pot multicomponent couplings; (iv) application of other efficient technologies such as microreactors and membrane separation processes; (v) efficient methodologies for the incorporation of readily available carbon and nitrogen sources such as CO_2, ammonia, glycerol, carbohydrates, amino acids, and biopolymers.

10. Acknowledgments

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11. References

(1) Eissen, M.; Metzger, J. O.; Schmidt, E.; Schneidewind, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 414–436.
(2) Afonso, C. A. M.,Crespo, J. G., Eds. *Green Separation Processes: Fundamentals and Applications*; Wiley-VCH: Weinheim, Germany, 2005.
(3) Tzschucke, C. C.; Markert, C.; Bannwarth, W.; Roller, S.; Hebel, A.; Haag, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3964–4000.
(4) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, U.K., 2000.
(5) Clark, J.; Afonso, C. A. M., Crespo, J. P. S. G., Eds.; Wiley-VCH: Weinheim, Germany, 2005.
(6) Eckert, C. A.; Liotta, C. L.; Bush, D.; Brown, J. S.; Hallett, J. P. *J. Phys. Chem. B* **2004**, *108*, 18108–18118.
(7) Reichardt, C. *Handbook of Solvents*; ChemTec Publishing: Toronto, 2001.
(8) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025–1074.
(9) Bougrin, K.; Loupy, A.; Soufiaoui, M. *J. Photochem. Photobiol. C: Photochem. Rev.* **2005**, *6*, 139–167.
(10) Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Chem. Commun.* **2001**, *n/a*, 2159–2169.
(11) de la Hoz, A.; Diaz-Ortis, A.; Moreno, A.; Langa, F. *Eur. J. Org. Chem.* **2000**, 3659–3673.
(12) Katritzky, A. R.; Singh, S. K. *Arkivoc* **2003**, 68–86.
(13) Varma, R. S. *Green Chem.* **1999**, *1*, 43–55.
(14) Varma, R. S. *Pure Appl. Chem.* **2001**, *73*, 193–198.
(15) Xu, Y.; Guo, Q. X. *Heterocycles* **2004**, *63*, 903–974.
(16) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, 1213–1234.
(17) Caddick, S. *Tetrahedron* **1995**, *51*, 10403–10432.
(18) Metzger, J. O. *Angew. Chem., Int. Ed.* **1998**, *37*, 2975–2978.
(19) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563–2591.
(20) Li, C. J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68–82.
(21) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751–2771.
(22) Breslow, R.; Maitra, U. *Tetrahedron Lett.* **1984**, *25*, 1239–1240.
(23) Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901–1904.
(24) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816–7817.
(25) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275–3279.
(26) Pirrung, M. C. *Chem.—Eur. J.* **2006**, *12*, 13121317..
(27) Pirrung, M. C.; Das Sarma, K. *Tetrahedron* **2005**, *61*, 11456–11472.
(28) Jung, Y. S.; Marcus, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492–5502.
(29) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Lillini, S.; Mantellini, F.; Santeusanio, S. *Synlett* **2005**, 1474–1476.
(30) Lubineau, A.; Auge, J. In *Modern Solvents in Organic Synthesis*; Knochel, P., Ed.; Springer: Berlin, 1999; Vol *206*.
(31) Lubineau, A.; Auge, J.; Queneau, Y. *Synthesis* **1994**, 741–760.
(32) Polshettiwar, V.; Varma, R. S. *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 723–737.
(33) Andrade, C. K. Z.; Alves, L. M. *Curr. Org. Chem.* **2005**, *9*, 195–218.
(34) Chen, J.; Spear, S. K.; Huddleston, J. G.; Rogers, R. D. *Green Chem.* **2005**, *7*, 64–82.
(35) Dickerson, T. J.; Reed, N. N.; Janda, K. D. *Chem. Rev.* **2002**, *102*, 3325–3343.
(36) Fan, Q. H.; Deng, G. J.; Chen, X. M.; Xie, W. C.; Jiang, D. Z.; Liu, D. S.; Chan, A. S. C. *J. Mol. Catal. A: Chem.* **2000**, *159*, 37–43.
(37) Fan, Q. H.; Deng, G. J.; Lin, C. C.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 1241–1247.
(38) Zhou, H. F.; Fan, Q. H.; Tang, W. J.; Xu, L. J.; He, Y. M.; Deng, G. J.; Zhao, L. W.; Gu, L. Q.; Chan, A. S. C. *Adv. Synth. Catal.* **2006**, *348*, 2172–2182.
(39) Harris, J. M. *Polyethylene Glycol Chemistry. Biotechnological and Biomedium Applications*; Plenum Press: New York, 1992.

(40) Harris, J. M.; Zalipsky, S. *Poly(ethylene glycol): Chemistry and Biological Applications*; American Chemical Society: Washington, DC, 1997.
(41) Fahrenkamp-Uppenbrink, J. *Science* **2002**, *297*, 798–798.
(42) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3773–3789.
(43) Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2083.
(44) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667–3691.
(45) Freemantle, M. *Chem. Eng. News* **2001**, *79*, 21–25.
(46) Larsen, A. S.; Holbrey, J. D.; Tham, F. S.; Reed, C. A. *J. Am. Chem. Soc.* **2000**, *122*, 7264–7272.
(47) Blanchard, L. A.; Hancu, D.; Beckman, E. J.; Brennecke, J. F. *Nature* **1999**, *399*, 28–29.
(48) Freemantle, M. *Chem. Eng. News* **1998**, *76*, 32–37.
(49) Hagiwara, R.; Ito, Y. *J. Fluor. Chem.* **2000**, *105*, 221–227.
(50) Sun, J.; Forsyth, M.; MacFarlane, D. R. *J. Phys. Chem. B* **1998**, *102*, 8858–8864.
(51) Miyatake, K.; Yamamoto, K.; Endo, K.; Tsuchida, E. *J. Org. Chem.* **1998**, *63*, 7522–7524.
(52) Kim, H. S.; Kim, Y. J.; Bae, J. Y.; Kim, S. J.; Lah, M. S.; Chin, C. S. *Organometallics* **2003**, *22*, 2498–2504.
(53) Bonhote, P.; Dias, A. P.; Papageorgiou, N.; Kalyanasundaram, K.; Gratzel, M. *Inorg. Chem.* **1996**, *35*, 1168–1178.
(54) Tait, S.; Osteryoung, R. A. *Inorg. Chem.* **1984**, *23*, 4352–4360.
(55) MacFarlane, D. R.; Meakin, P.; Sun, J.; Amini, N.; Forsyth, M. *J. Phys. Chem. B* **1999**, *103*, 4164–4170.
(56) Davis, J. H.; Forrester, K. J. *Tetrahedron Lett.* **1999**, *40*, 1621–1622.
(57) Vestergaard, B.; Bjerrum, N. J.; Petrushina, I.; Hjuler, H. A.; Berg, R. W.; Begtrup, M. *J. Electrochem. Soc.* **1993**, *140*, 3108–3113.
(58) Tomoharu, N. (Sanyo Chemical Ind. Ltd.) Japanese Patent JP11273734, 1999.
(59) Mamantov, G.; Caja, J.; Dunstan, T. D. J. Electrochemical Systems Inc., 1996.
(60) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Zanatta, N.; Bonacorso, H. G. *Chem. Rev.* **2008**, *108*, 2015–2050.
(61) Vogt, M. Ph.D. Thesis, Technische Hochschule, 1991.
(62) Horvath, I. T.; Rabai, J. *Science* **1994**, *266*, 72–75.
(63) Curran, D. P. *Aldrichim. Acta* **2006**, *39*, 3–9.
(64) Hope, E. G.; Stuart, A. M. *J. Fluor. Chem.* **1999**, *100*, 75–83.
(65) Barthel-Rosa, L. P.; Gladysz, J. A. *Coord. Chem. Rev.* **1999**, *192*, 587–605.
(66) Cornils, B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2057–2059.
(67) Curran, D. P. *Pure Appl. Chem.* **2000**, *72*, 1649–1653.
(68) Horvath, I. T. *Acc. Chem. Res.* **1998**, *31*, 641–650.
(69) Ravishankara, A. R.; Turnipseed, A. A.; Jensen, N. R.; Barone, S.; Mills, M.; Howard, C. J.; Solomon, S. *Science* **1994**, *263*, 71–75.
(70) Matsugi, M.; Curran, D. P. *Org. Lett.* **2004**, *6*, 2717–2720.
(71) Wende, M.; Gladysz, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 5861–5872.
(72) Zhang, W.; Lu, Y. M. *J. Comb. Chem.* **2006**, *8*, 890–896.
(73) Zhang, W.; Lu, Y. *J. Comb. Chem.* **2007**, *9*, 836–843.
(74) Yoshida, J.; Itami, K. *Chem. Rev.* **2002**, *102*, 3693–3716.
(75) Zhang, W.; Curran, D. P. *Tetrahedron* **2006**, *62*, 11837–11865.
(76) Dinh, L. V.; Gladysz, J. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4095–4097.
(77) Gladysz, J. A., Curran J. A., Horváth, I. T., Eds. *Handbook of Fluorous Chemistry*; Wiley-VCH: Weinheim, Germany, 2004.
(78) Hiroshi Matsubara, H.; Ilhyong Ryu, I.; Afonso, C. A. M., Crespo, J. G., Eds.; Wiley-VCH: Weinheim, Germany, 2005.
(79) Dandapani, S. *QSAR Comb. Sci.* **2006**, *25*, 681–688.
(80) Zhang, W. *Chem. Rev.* **2004**, *104*, 2531–2556.
(81) Jessop, P. G.; Ikariya, T.; Noyori, R. *Chem. Rev.* **1999**, *99*, 475–493.
(82) Osuna, A. B.; Šerbanović, A.; Ponte, M. N. d.; Afonso, C. A. M., Crespo, J. P. S. G., Eds.; Wiley-VCH: Weinheim, Germany, 2005.
(83) Baiker, A. *Chem. Rev.* **1999**, *99*, 453–473.
(84) Matsuda, T.; Watanabe, K.; Harada, T.; Nakamura, K. *Catal. Today* **2004**, *96*, 103–111.
(85) Leitner, W. *Acc. Chem. Res.* **2002**, *35*, 746–756.
(86) Kano, D.; Minakata, S.; Komatsu, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3186–3188.
(87) Fioravanti, S.; Pellacani, L.; Stabile, S.; Tardella, P. A.; Ballini, R. *Tetrahedron* **1998**, *54*, 6169–6176.
(88) Jain, S. L.; Joseph, J. K.; Sain, B. *J. Mol. Catal. A: Chem.* **2006**, *256*, 16–20.
(89) Attanasi, O. A.; Davoli, P.; Favi, G.; Filippone, P.; Forni, A.; Moscatelli, G.; Prati, F. *Org. Lett.* **2007**, *9*, 3461–3464.
(90) Yadav, L. D. S.; Kapoor, R. *Synthesis* **2002**, 2344–2346.
(91) Bieber, L. W.; de Araujo, M. C. F. *Molecules* **2002**, *7*, 902–906.
(92) Mekonnen, A.; Carlson, R. *Tetrahedron* **2006**, *62*, 852–856.
(93) Das, B.; Reddy, V. S.; Krishnaiah, M. *Tetrahedron Lett.* **2006**, *47*, 8471–8473.
(94) Zhang, J. L.; Che, C. M. *Org. Lett.* **2002**, *4*, 1911–1914.
(95) Zhang, J. L.; Huang, J. S.; Che, C. M. *Chem.—Eur. J.* **2006**, *12*, 3020–3031.
(96) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701–2743.
(97) Yadav, J. S.; Reddy, B. V. S.; Reddy, P. N.; Rao, M. S. *Synthesis* **2003**, 1387–1390.
(98) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844–6845.
(99) Antunes, A. M. M.; Marto, S. J. L.; Branco, P. S.; Prabhakar, S.; Lobo, A. M. *Chem. Commun.* **2001**, 405–406.
(100) Chanda, B. M.; Vyas, R.; Bedekar, A. V. *J. Org. Chem.* **2001**, *66*, 30–34.
(101) Liang, J. L.; Yu, X. Q.; Che, C. M. *Chem. Commun.* **2002**, 124–125.
(102) Cho, D. J.; Jeon, S. J.; Kim, H. S.; Cho, C. S.; Shim, S. C.; Kim, T. J. *Tetrahedron: Asymmetry* **1999**, *10*, 3833–3848.
(103) Rasmussen, K. G.; Jorgensen, K. A. *J. Chem. Soc., Chem. Commun.* **1995**, 1401–1402.
(104) Xie, W. H.; Fang, J. W.; Li, J.; Wang, P. G. *Tetrahedron* **1999**, *55*, 12929–12938.
(105) Casarrubios, L.; Perez, J. A.; Brookhart, M.; Templeton, J. L. *J. Org. Chem.* **1996**, *61*, 8358–8359.
(106) Sengupta, S.; Mondal, S. *Tetrahedron Lett.* **2000**, *41*, 6245–6248.
(107) Zhu, Z. L.; Espenson, J. H. *J. Am. Chem. Soc.* **1996**, *118*, 9901–9907.
(108) Sun, W.; Xia, C. G.; Wang, H. W. *Tetrahedron Lett.* **2003**, *44*, 2409–2411.
(109) Yadav, J. S.; Reddy, B. V. S.; Reddy, C. S.; Rajasekhar, K. *J. Org. Chem.* **2003**, *68*, 2525–2527.
(110) Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177–6215.
(111) Martelli, G.; Spunta, G.; Panunzio, M. *Tetrahedron Lett.* **1998**, *39*, 6257–6260.
(112) Benaglia, M.; Cozzi, F.; Puglisi, A. *Eur. J. Org. Chem.* **2007**, 2865–2869.
(113) Dandia, A.; Singh, R.; Sharma, P. *Heteroat. Chem.* **2003**, *14*, 468–473.
(114) Bose, A. K.; Jayaraman, M.; Okawa, A.; Bari, S. S.; Robb, E. W.; Manhas, M. S. *Tetrahedron Lett.* **1996**, *37*, 6989–6992.
(115) Kidwai, M.; Misra, P.; Bhushan, K. R.; Saxena, R. K.; Singh, M. *Monatsh. Chem.* **2000**, *131*, 937–943.
(116) Nivsarkar, M.; Kaushik, M. P. *Catal. Commun.* **2005**, *6*, 367–370.
(117) Yadav, L. D. S.; Kapoor, R. *Synthesis* **2002**, 1502–1504.
(118) Loh, T. P.; Chua, G. L. *Chem. Commun.* **2006**, 2739–2749.
(119) Jayaraman, M.; Batista, M. T.; Manhas, M. S.; Bose, A. K. *Heterocycles* **1998**, *49*, 97–100.
(120) Jayaraman, M.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1997**, *38*, 709–712.
(121) Cho, Y. S.; Lee, J. E.; Pae, A. N.; Choi, K. I.; Koh, H. Y. *Tetrahedron Lett.* **1999**, *40*, 1725–1728.
(122) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Org. Lett.* **2000**, *2*, 1411–1414.
(123) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Rodriguez-Acebes, R. *J. Org. Chem.* **2001**, *66*, 5208–5216.
(124) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Rodriguez-Acebes, R. *Synthesis* **2003**, 1163–1170.
(125) Alcaide, B.; Almendros, P.; Rodriguez-Acebes, R. *J. Org. Chem.* **2002**, *67*, 1925–1928.
(126) Alcaide, B.; Almendros, P.; Rodriguez-Acebes, R. *J. Org. Chem.* **2005**, *70*, 2713–2719.
(127) Pirrung, M. C.; Das Sarma, K. *Synlett* **2004**, 1425–1427.
(128) Candeias, N. R.; Gois, P. M. P.; Afonso, C. A. M. *Chem. Commun.* **2005**, 391–393.
(129) Candeias, N. R.; Gois, P. M. P.; Afonso, C. A. M. *J. Org. Chem.* **2006**, *71*, 5489–5497.
(130) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. *Chem.—Eur. J.* **2000**, *6*, 133–138.
(131) Molteni, V.; Annunziata, R.; Cinquini, M.; Cozzi, F.; Benaglia, M. *Tetrahedron Lett.* **1998**, *39*, 1257–1260.
(132) Shou, W. G.; Yang, Y. Y.; Wang, Y. G. *Synthesis* **2005**, 530–536.
(133) Jian, S. Z.; Yuan, Q.; Wang, Y. G. *Synthesis* **2006**, 1829–1835.
(134) Gois, P. M. P.; Afonso, C. A. M. *Tetrahedron Lett.* **2003**, *44*, 6571–6573.
(135) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063–3070.
(136) Padwa, A. *J. Organomet. Chem.* **2001**, *617*, 3–16.
(137) Mehta, G.; Muthusamy, S. *Tetrahedron* **2002**, *58*, 9477–9504.
(138) Taber, D. F.; Ruckle, R. E. *J. Am. Chem. Soc.* **1986**, *108*, 7686–7693.
(139) Danks, T. N. *Tetrahedron Lett.* **1999**, *40*, 3957–3960.
(140) Abid, M.; Spaeth, A.; Torok, B. *Adv. Synth. Catal.* **2006**, *348*, 2191–2196.

(141) Curini, M.; Montanari, F.; Rosati, O.; Lioy, E.; Margarita, R. *Tetrahedron Lett.* **2003**, *44*, 3923–3925.
(142) Chen, J. X.; Wu, H. Y.; Zheng, Z. G.; Jin, C.; Zhang, X. X.; Su, W. K. *Tetrahedron Lett.* **2006**, *47*, 5383–5387.
(143) Jolivet-Fouchet, S.; Hamelin, J.; Texier-Boullet, F.; Toupet, L.; Jacquault, P. *Tetrahedron* **1998**, *54*, 4561–4578.
(144) Jolivet, S.; Toupet, L.; TexierBoullet, F.; Hamelin, J. *Tetrahedron* **1996**, *52*, 5819–5832.
(145) Ranu, B. C.; Hajra, A. *Tetrahedron* **2001**, *57*, 4767–4773.
(146) Kidwai, M.; Singhal, K.; Kukreja, S. *Heteroat. Chem.* **2007**, *18*, 617–621.
(147) Ranu, B. C.; Hajra, A.; Jana, U. *Synlett* **2000**, 75–76.
(148) Aydogan, F.; Demir, A. S. *Tetrahedron* **2005**, *61*, 3019–3023.
(149) Trofimov, B. A.; Stepanova, Z. V.; Sobenina, L. N.; Mikhaleva, A. I.; Ushakov, I. A. *Tetrahedron Lett.* **2004**, *45*, 6513–6516.
(150) Trofimov, B. A.; Gusarova, N. K.; Sukhov, B. G.; Malysheva, S. F.; Tarasova, O. A.; Belogorlova, N. A.; Maximova, M. A.; Tunik, S. P. *Synthesis* **2005**, 965–970.
(151) Prauda, I.; Greiner, I.; Ludanyi, K.; Keglevich, G. *Synth. Commun.* **2007**, *37*, 317–322.
(152) Dessole, G.; Herrera, R. P.; Ricci, A. *Synlett* **2004**, 2374–2378.
(153) Bogdal, D.; Pielichowski, J.; Boron, A. *Synlett* **1996**, 873–874.
(154) Bogdal, D.; Pielichowski, J.; Jaskot, K. *Heterocycles* **1997**, *45*, 715–722.
(155) Shaabani, A.; Dabiri, M.; Bazgir, A.; Gharanjig, K. *Dyes Pigm.* **2006**, *71*, 68–72.
(156) Pospisil, J.; Potacek, M. *Eur. J. Org. Chem.* **2004**, 710–716.
(157) Pospisil, J.; Potacek, M. *Tetrahedron* **2007**, *63*, 337–346.
(158) Jayashankaran, J.; Manian, R. D. R. S.; Raghunathan, R. *Tetrahedron Lett.* **2004**, *45*, 7303–7305.
(159) Manian, R. D. R. S.; Jayashankaran, J.; Raghunathan, R. *Tetrahedron* **2006**, *62*, 12357–12362.
(160) Matsumura, Y.; Ikeda, T.; Onomura, O. *Heterocycles* **2006**, *67*, 113–117.
(161) de Godoy, L. A. F.; Camilo, N. S.; Pilli, R. A. *Tetrahedron Lett.* **2006**, *47*, 7853–7856.
(162) Narayan, S.; Seelhammer, T.; Gawley, R. E. *Tetrahedron Lett.* **2004**, *45*, 757–759.
(163) Varma, R. S.; Dahiya, R.; Kumar, S. *Tetrahedron Lett.* **1997**, *38*, 2039–2042.
(164) Varma, R. S.; Dahiya, R. *Synlett* **1997**, 1245–1246.
(165) Karthikeyan, S. V.; Perumal, S.; Balasubramanian, K. K. *Tetrahedron Lett.* **2007**, *48*, 6133–6136.
(166) Bogdal, D.; Pielichowski, J.; Jaskot, K. *Synth. Commun.* **1997**, *27*, 1553–1560.
(167) Kamal, A.; Reddy, B. S. N.; Reddy, G. S. K. *Synlett* **1999**, 1251–1252.
(168) Kiryanov, A. A.; Sampson, P.; Seed, A. J. *J. Org. Chem.* **2001**, *66*, 7925–7929.
(169) Markovic, R.; Pergal, M. M.; Baranac, M.; Stanisavljev, D.; Stojanovic, M. *Arkivoc* **2006**, 83–90.
(170) Kuhnert, N.; Danks, T. N. *Green Chem.* **2001**, *3*, 68–70.
(171) García-Tellado, F.; Loupy, A.; Petit, A.; Marrero-Terrero, A. L. *Eur. J. Org. Chem.* **2003**, 4387–4391.
(172) Marrero-Terrero, A. L.; Loupy, A. *Synlett* **1996**, 245–246.
(173) Boruah, A.; Baruah, B.; Prajapati, D.; Sandhu, J. S.; Ghosh, A. C. *Tetrahedron Lett.* **1996**, *37*, 4203–4204.
(174) Baruah, B.; Prajapati, D.; Boruah, A.; Sandhu, J. S. *Synth. Commun.* **1997**, *27*, 2563–2567.
(175) Fraga-Dubreuil, J.; Cherouvrier, J. R.; Bazureau, J. P. *Green Chem.* **2000**, *2*, 226–229.
(176) Lerestif, J. M.; Toupet, L.; Sinbandhit, S.; Tonnard, F.; Bazureau, J. P.; Hamelin, J. *Tetrahedron* **1997**, *53*, 6351–6364.
(177) Cheng, Q.; Zhang, W.; Tagami, Y.; Oritani, T. *J. Chem. Soc., Perkin Trans. 1* **2001**, 452–456.
(178) Loupy, A.; Petit, A.; Bonnet-Delpon, D. *J. Fluor. Chem.* **1995**, *75*, 215–216.
(179) Reddy, G. V.; Rao, G. V.; Iyengar, D. S. *Synth. Commun.* **1999**, *29*, 4071–4077.
(180) Hamidian, H.; Tikdari, A. M. *Heterocycl. Commun.* **2006**, *12*, 29–34.
(181) Salehi, P.; Dabiri, M.; Khosropour, A. R.; Roozbehniya, P. *J. Iran. Chem. Soc.* **2006**, *3*, 98–104.
(182) Yu, C. M.; Zhou, B. C.; Su, W. K.; Xu, Z. Y. *Synth. Commun.* **2006**, *36*, 3447–3453.
(183) Chandrasekhar, S.; Karri, P. *Tetrahedron Lett.* **2007**, *48*, 785–786.
(184) Lee, J. C.; Choi, H. J.; Lee, Y. C. *Tetrahedron Lett.* **2003**, *44*, 123–125.
(185) Lee, J. C.; Seo, J. W.; Baek, J. W. *Synth. Commun.* **2007**, *37*, 2159–2162.
(186) Loupy, A.; Regnier, S. *Tetrahedron Lett.* **1999**, *40*, 6221–6224.
(187) Syassi, B.; Bougrin, K.; Soufiaoui, M. *Tetrahedron Lett.* **1997**, *38*, 8855–8858.
(188) Touaux, B.; Texier-Boullet, F.; Hamelin, J. *Heteroat. Chem.* **1998**, *9*, 351–354.
(189) Mabrour, M.; Bougrin, K.; Benhida, R.; Loupy, A.; Soufiaoui, M. *Tetrahedron Lett.* **2007**, *48*, 443–447.
(190) Bigdeli, M. A.; Mahdavinia, G. H.; Jafari, S. *J. Chem. Res.* **2007**, 26–28.
(191) Yadav, L. D. S.; Rai, V. K. *Tetrahedron* **2006**, *62*, 8029–8034.
(192) Varma, R. S. *J. Heterocycl. Chem.* **1999**, *36*, 1565–1571.
(193) Bougrin, K.; Loupy, A.; Soufiaoui, M. *Tetrahedron* **1998**, *54*, 8055–8064.
(194) Abdel-Latif, E.; Metwally, M. A. *Monatsh. Chem.* **2007**, *138*, 771–776.
(195) Kasmi, S.; Hamelin, J.; Benhaoua, H. *Tetrahedron Lett.* **1998**, *39*, 8093–8096.
(196) Xia, M.; Lu, Y. D. *Synth. Commun.* **2006**, *36*, 1637–1643.
(197) Kasmi-Mir, S.; Djafri, A.; Paquin, L.; Hamelin, J.; Rahmouni, M. *Molecules* **2006**, *11*, 597–602.
(198) Heravi, M. M.; Nami, N.; Oskooie, H. A.; Hekmatshoar, R. *Phosphorus, Sulfur Silicon Relat. Elem.* **2006**, *181*, 87–91.
(199) Bourahla, K.; Derdour, A.; Rahmouni, M.; Carreaux, F.; Bazureau, J. P. *Tetrahedron Lett.* **2007**, *48*, 5785–5789.
(200) Darehkordi, A.; Saidi, K.; Islami, M. R. *Arkivoc* **2007**, *1*, 180–188.
(201) Deetlefs, M.; Seddon, K. R. *Green Chem.* **2003**, *5*, 181–186.
(202) Zhuang, W.; Jorgensen, K. A. *Chem. Commun.* **2002**, 1336–1337.
(203) Khalili, B.; Jajarmi, P.; Eftekhari-Sis, B.; Hashemi, M. M. *J. Org. Chem.* **2008**, *73*, 2090–2095.
(204) Yavari, I.; Sabbaghan, M. *Synth. Commun.* **2007**, *37*, 1791–1800.
(205) Manabe, K.; Iimura, S.; Sun, X. M.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 11971–11978.
(206) Hiroto, S.; Shinokubo, H.; Osuka, A. *J. Am. Chem. Soc.* **2006**, *128*, 6568–6569.
(207) Lindstrom, U. M.; Ding, R.; Hidestal, O. *Chem. Commun.* **2005**, 1773–1774.
(208) Ju, Y. H.; Varma, R. S. *Org. Lett.* **2005**, *7*, 2409–2411.
(209) Fuji, K.; Morimoto, T.; Tsutsumi, K.; Kakiuchi, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 2409–2411.
(210) Yorimitsu, H.; Wakabayashi, K.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1963–1970.
(211) Miyabe, H.; Ueda, M.; Fujii, K.; Nishimura, A.; Naito, T. *J. Org. Chem.* **2003**, *68*, 5618–5626.
(212) Miyabe, H.; Ueda, M.; Naito, T. *J. Org. Chem.* **2000**, *65*, 5043–5047.
(213) Binder, J. B.; Guzei, I. A.; Raines, R. T. *Adv. Synth. Catal.* **2007**, *349*, 395–404.
(214) Rao, H. S. P.; Jothilingam, S. *Tetrahedron Lett.* **2001**, *42*, 6595–6597.
(215) Rao, H. S. P.; Jothilingam, S.; Scheeren, H. W. *Tetrahedron* **2004**, *60*, 1625–1630.
(216) Zhang, H. Q.; Yang, G. C.; Chen, J. N.; Chen, Z. X. *Synthesis* **2004**, 3055–3059.
(217) Yao, Q. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3896–3901.
(218) Wipf, P.; Venkatraman, S. *Tetrahedron Lett.* **1996**, *37*, 4659–4662.
(219) Serra, G.; Mahler, G.; Manta, E. *Heterocycles* **1998**, *48*, 2035–2048.
(220) Shang, Y. J.; Wang, Y. G. *Synthesis* **2002**, 1663–1668.
(221) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Lillini, S.; Mantellini, F.; Santeusanio, S. *Org. Lett.* **2005**, *7*, 2469–2471.
(222) Jones, A. *Pyrroles*; Wiley: New York, 1990.
(223) Jones, A.; Bean, G. P. *The Chemistry of Pyrroles*; Academic Press: London, 1977.
(224) Ranu, B. C.; Dey, S. S. *Tetrahedron Lett.* **2003**, *44*, 2865–2868.
(225) Sreekumar, R.; Padmakumar, R. *Synth. Commun.* **1998**, *28*, 1661–1665.
(226) Texierboullet, F.; Klein, B.; Hamelin, J. *Synthesis* **1986**, 409–411.
(227) Ballini, R.; Barboni, L.; Bosica, G.; Petrini, M. *Synlett* **2000**, 391–393.
(228) Khanna, I. K.; Weier, R. M.; Yu, Y.; Collins, P. W.; Miyashiro, J. M.; Koboldt, C. M.; Veenhuizen, A. W.; Currie, J. L.; Seibert, K.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1619–1633.
(229) Raghavan, S.; Anuradha, K. *Synlett* **2003**, 711–713.
(230) Yu, S. X.; Lequesne, P. W. *Tetrahedron Lett.* **1995**, *36*, 6205–6208.
(231) Wang, B.; Gu, Y. L.; Luo, C.; Yang, T.; Yang, L. M.; Suo, J. S. *Tetrahedron Lett.* **2004**, *45*, 3417–3419.
(232) Yadav, J. S.; Reddy, B. V. S.; Eeshwaraiah, B.; Gupta, M. K. *Tetrahedron Lett.* **2004**, *45*, 5873–5876.
(233) Candy, C. F.; Jones, R. A *J. Org. Chem* **1971**, *36*, 3993-&.
(234) Hobbs, C. F.; McMillin, C. K.; Papadopoulos, E. P.; VanderWerf, C. A. *J. Am. Chem. Soc* **1962**, *84*, 43–51.
(235) Guida, W. C.; Mathre, D. J. *J. Org. Chem.* **1980**, *45*, 3172–3176.
(236) Le, Z. G.; Chen, Z. C.; Hu, Y.; Zheng, Q. G. *Synthesis* **2004**, 1951–1954.
(237) Yavari, I.; Kowsari, E. *Synlett* **2008**, 897–899.
(238) Jorapur, Y. R.; Lee, C. H.; Chi, D. Y. *Org. Lett.* **2005**, *7*, 1231–1234.

(239) Schofield, K. *Heteroaromatic Nitrogen Compounds: Pyrroles and Pyridines*; Plenum Press: New York, 1967.
(240) Joule, J. A.; Mills, K.; Smith, G. F. *Heterocyclic Chemistry*; Chapman & Hall: London, 1995.
(241) Baltazzi, E *Chem. Rev* **1963**, *63*, 511–556.
(242) Nicolaou, K. C.; Claremon, D. A.; Papahatjis, D. P. *Tetrahedron Lett.* **1981**, *22*, 4647–4650.
(243) Patterson, J.M.; Soedigdo, S *J. Org. Chem* **1968**, *33*, 2057–2061.
(244) Jorapur, Y. R.; Jeong, J. M.; Chi, D. Y. *Tetrahedron Lett.* **2006**, *47*, 2435–2438.
(245) Rodriquez, M.; Bassarello, C.; Bifulco, G.; Gomez-Paloma, L.; Mann, A.; Marchetti, M.; Schoenfelder, A.; Taddei, M. *Synlett* **2005**, 1581–1585.
(246) Brehm, L.; Greenwood, J. R.; Hansen, K. B.; Nielsen, B.; Egebjerg, J.; Stensbol, T. B.; Brauner-Osborne, H.; Slok, F. A.; Kronborg, T. T. A.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2003**, *46*, 1350–1358.
(247) Konno, K.; Hashimoto, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *J. Am. Chem. Soc.* **1988**, *110*, 4807–4815.
(248) Pilli, R. A.; Robello, L. G.; Camilo, N. S.; Dupont, J.; Lapis, A. A. M.; Neto, B. A. D. *Tetrahedron Lett.* **2006**, *47*, 1669–1672.
(249) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817–3856.
(250) Camilo, N. S.; Pilli, R. A. *Tetrahedron Lett.* **2004**, *45*, 2821–2823.
(251) Pilli, R. A.; Robello, L. G. *Synlett* **2005**, 2297–2300.
(252) Xu, L. W.; Li, L.; Xia, C. G.; Zhou, S. L.; Li, J. W. *Tetrahedron Lett.* **2004**, *45*, 1219–1221.
(253) Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 853–854.
(254) Giles, R. G.; Lewis, N. J.; Quick, J. K.; Sasse, M. J.; Urquhart, M. W. J.; Youssef, L. *Tetrahedron* **2000**, *56*, 4531–4537.
(255) Grant, E. B.; Guiadeen, D.; Baum, E. Z.; Foleno, B. D.; Jin, H. Y.; Montenegro, D. A.; Nelson, E. A.; Bush, K.; Hlasta, D. J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2179–2182.
(256) Yang, D. H.; Chen, Z. C.; Chen, S. Y.; Zheng, Q. G. *Synthesis* **2003**, 1891–1894.
(257) Bailleux, V.; Vallee, L.; Nuyts, J. P.; Vamecq, J. *Chem. Pharm. Bull.* **1994**, *42*, 1817–1821.
(258) Shibata, Y.; Sasaki, K.; Hashimoto, Y.; Iwasaki, S. *Chem. Pharm. Bull.* **1996**, *44*, 156–162.
(259) Jayakumar, R.; Balaji, R.; Nanjundan, S. *Eur. Polym. J.* **2000**, *36*, 1659–1666.
(260) Chandrasekhar, S.; Padmaja, M. B.; Raza, A. *Synlett* **1999**, 1597–1599.
(261) Mhaske, S. B.; Argade, N. P. *Synthesis* **2003**, 863–870.
(262) Liu, R. Y.; Zhang, P. W.; Gan, T.; Cook, J. M. *J. Org. Chem.* **1997**, *62*, 7447–7456.
(263) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757–761.
(264) Mohri, K.; Suzuki, K.; Usui, M.; Isobe, K.; Tsuda, Y. *Chem. Pharm. Bull.* **1995**, *43*, 159–161.
(265) Garner, P.; Ho, W. B.; Grandhee, S. K.; Youngs, W. J.; Kennedy, V. O. *J. Org. Chem.* **1991**, *56*, 5893–5903.
(266) Kalgutkar, A. S.; Crews, B. C.; Marnett, L. J. *J. Med. Chem.* **1996**, *39*, 1692–1703.
(267) Meyers, A. I.; Lefker, B. A.; Sowin, T. J.; Westrum, L. J. *J. Org. Chem.* **1989**, *54*, 4243–4246.
(268) Miyachi, H.; Azuma, A.; Ogasawara, A.; Uchimura, E.; Watanabe, N.; Kobayashi, Y.; Kato, F.; Kato, M.; Hashimoto, Y. *J. Med. Chem.* **1997**, *40*, 2858–2865.
(269) Le, Z. G.; Chen, Z. C.; Hu, Y.; Zheng, Q. G. *Synthesis* **2004**, 995–998.
(270) Chapman, J. M.; Voorstad, P. J.; Cocolas, G. H.; Hall, I. H. *J. Med. Chem.* **1983**, *26*, 237–243.
(271) Hubbard, J. L.; Carl, J. M.; Anderson, G. D.; Rankin, G. O. *J. Heterocycl. Chem.* **1992**, *29*, 719–721.
(272) Jeong, I. Y.; Lee, W. S.; Goto, S.; Sano, S.; Shiro, M.; Nagao, Y. *Tetrahedron* **1998**, *54*, 14437–14454.
(273) Arnold, L. D.; Assil, H. I.; Vederas, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 3973–3976.
(274) Crich, D.; Hao, X.; Lucas, M. *Tetrahedron* **1999**, *55*, 14261–14268.
(275) Crich, D.; Hao, X. L.; Lucas, M. A. *Org. Lett.* **1999**, *1*, 269–271.
(276) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140.
(277) Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3760–3765.
(278) Clavier, H.; Grela, K.; Kirschning, A.; Mauduit, M.; Nalon, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 6786–6801.
(279) Yao, Q. W.; Zhang, Y. L. *J. Am. Chem. Soc.* **2004**, *126*, 74–75.
(280) Matsugi, M.; Curran, D. P. *J. Org. Chem.* **2005**, *70*, 1636–1642.
(281) Michalek, F.; Bannwarth, W. *Helv. Chim. Acta* **2006**, *89*, 1030–1037.
(282) da Costa, R. C.; Gladysz, J. A. *Adv. Synth. Catal.* **2007**, *349*, 243–254.
(283) Grigg, R.; York, M. *Tetrahedron Lett.* **2000**, *41*, 7255–7258.
(284) Furstner, A.; Koch, D.; Langemann, K.; Leitner, W.; Six, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2466–2469.
(285) Furstner, A.; Ackermann, L.; Beck, K.; Hori, H.; Koch, D.; Langemann, K.; Liebl, M.; Six, C.; Leitner, W. *J. Am. Chem. Soc.* **2001**, *123*, 9000–9006.
(286) Werner, S.; Curran, D. P. *Org. Lett.* **2003**, *5*, 3293–3296.
(287) Studer, A.; Curran, D. P. *Tetrahedron* **1997**, *53*, 6681–6696.
(288) Curran, D. P.; Hadida, S.; Kim, S.-Y. *Tetrahedron* **1999**, *55*, 8997–9006.
(289) Hein, J. E.; Geary, L. M.; Jaworski, A. A.; Hultin, P. G. *J. Org. Chem.* **2005**, *70*, 9940–9946.
(290) Nakamura, Y.; Okumura, K.; Kojima, M.; Takeuchi, S. *Tetrahedron Lett.* **2006**, *47*, 239–243.
(291) Sakanishi, K.; Obata, H.; Mochida, I.; Sakaki, T.; Shibata, M. *J. Supercrit. Fluids* **1998**, *13*, 203–210.
(292) Zevenhoven, R.; Eloneva, S.; Teir, S. *Catal. Today* **2006**, *115*, 73–79.
(293) Omae, I. *Catal. Today* **2006**, *115*, 33–52.
(294) Sakakura, T.; Choi, J. C.; Yasuda, H. *Chem. Rev.* **2007**, *107*, 2365–2387.
(295) Matsuda, T.; Ohashi, Y.; Harada, T.; Yanagihara, R.; Nagasawa, T.; Nakamura, K. *Chem. Commun.* **2001**, 2194–2195.
(296) Maggi, R.; Bertolotti, C.; Orlandini, E.; Oro, C.; Sartori, G.; Selva, M. *Tetrahedron Lett.* **2007**, *48*, 2131–2134.
(297) Jouneau, S.; Bazureau, J. P. *Tetrahedron Lett.* **1999**, *40*, 8097–8098.
(298) Ponnala, S.; Kumar, S.; Bhat, B. A.; Sahu, D. P. *Synth. Commun.* **2005**, *35*, 901–906.
(299) Balalaie, S.; Arabanian, A.; Hashtroudi, M. S. *Monatsh. Chem.* **2000**, *131*, 945–948.
(300) Balalaie, S.; Arabanian, A. *Green Chem.* **2000**, *2*, 274–276.
(301) Usyatinsky, A. Y.; Khmelnitsky, Y. L. *Tetrahedron Lett.* **2000**, *41*, 5031–5034.
(302) Nagarapu, L.; Apuri, S.; Kantevari, S. *J. Mol. Catal. A: Chem.* **2007**, *266*, 104–108.
(303) Balalaie, S.; Hashemi, M. M.; Akhbari, M. *Tetrahedron Lett.* **2003**, *44*, 1709–1711.
(304) Xu, Y.; Liu, Y. Z.; Rui, L.; Liu, L.; Guo, Q. X. *Heterocycles* **2004**, *63*, 87-+.
(305) Xu, Y.; Wan, L. F.; Salehi, H.; Deng, W.; Guo, Q. X. *Heterocycles* **2004**, *63*, 1613–1618.
(306) Karimi, A. R.; Alimohammadi, Z.; Azizian, J.; Mohammadi, A. A.; Mohammadizadeh, M. R. *Catal. Commun.* **2006**, *7*, 728–732.
(307) Kantevari, S.; Vuppalapati, S. V. N.; Biradar, D. O.; Nagarapu, L. *J. Mol. Catal. A: Chem.* **2007**, *266*, 109–113.
(308) Kidwai, M.; Saxena, S.; Ruby; Rastogi, S. *Bull. Korean Chem. Soc.* **2005**, *26*, 2051–2053.
(309) Shaabani, A.; Rahmati, A.; Farhangi, E.; Badri, Z. *Catal. Commun.* **2007**, *8*, 1149–1152.
(310) Alcázar, J.; Begtrup, M.; De La Hoz, A. *Heterocycles* **1996**, *43*, 1465–1470.
(311) Tao, X. L.; Lei, M.; Wang, Y. G. *Synth. Commun.* **2007**, *37*, 399–408.
(312) Varma, R. S.; Namboodiri, V. V. *Chem. Commun.* **2001**, 643–644.
(313) Varma, R. S.; Namboodiri, V. V. *Pure Appl. Chem.* **2001**, *73*, 1309–1313.
(314) Namboodiri, V. V.; Varma, R. S. *Org. Lett.* **2002**, *4*, 3161–3163.
(315) Perozo-Rondon, E.; Costarrosa, L.; Martin-Aranda, R. M.; Rojas-Cervantes, M. L.; Vicente-Rodriguez, M. A. *Appl. Surf. Sci.* **2006**, *252*, 6067–6070.
(316) Xie, Y. X.; Pi, S. F.; Wang, J.; Yin, L.; Li, J. H. *J. Org. Chem.* **2006**, *71*, 8324–8327.
(317) Torregrosa, R.; Pastor, I. M.; Yus, M. *Tetrahedron* **2007**, *63*, 469–473.
(318) Varma, R. S.; Kumar, D. *Tetrahedron Lett.* **1999**, *40*, 7665–7669.
(319) Zhao, N.; Wang, Y. L.; Wang, J. Y. *J. Chin. Chem. Soc.* **2005**, *52*, 535–538.
(320) Wang, R.; Lu, X. X.; Yu, X. Q.; Shi, L.; Sun, Y. *J. Mol. Catal. A: Chem.* **2007**, *266*, 198–201.
(321) Bougrin, K.; Soufiaoui, M. *Tetrahedron Lett.* **1995**, *36*, 3683–3686.
(322) Villemin, D.; Hammadi, M.; Martin, B. *Synth. Commun.* **1996**, *26*, 2895–2899.
(323) Mobinikhaledi, A.; Zendehdel, M.; Jamshidi, F. H. *Synth. React. Inorg., Met.-Org., Nano-Met. Chem.* **2007**, *37*, 175–177.
(324) Reddy, G.V.; Rao, V. V. V. N. S. R.; Narsaiah, B.; Rao, P. S. *Synth. Commun* **2002**, *32*, 2467–2476.
(325) Navarrete-Vazquez, G.; Moreno-Diaz, H.; Aguirre-Crespo, F.; Leon-Rivera, I.; Villalobos-Molina, R.; Munoz-Muniz, O.; Estrada-Soto, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4169–4173.
(326) Navarrete-Vazquez, G.; Moreno-Diaz, H.; Estrada-Soto, S.; Torres-Piedra, M.; Leon-Rivera, I.; Tlahuext, H.; Munoz-Muniz, O.; Torres-Gomez, H. *Synth. Commun.* **2007**, *37*, 2815–2825.
(327) Nagawade, R. R.; Shinde, D. B. *Chin. Chem. Lett.* **2006**, *17*, 453–456.
(328) Trivedi, R.; De, S. K.; Gibbs, R. A. *J. Mol. Catal. A: Chem.* **2006**, *245*, 8–11.

(329) Mohammadpoor-Baltork, I.; Khosropour, A. R.; Hojati, S. F. *Monatsh. Chem.* **2007**, *138*, 663–667.
(330) Moghaddam, F. M.; Bardajee, G. R.; Ismaili, H.; Taimoory, S. M. D. *Synth. Commun.* **2006**, *36*, 2543–2548.
(331) Moghaddam, F. M.; Ismaili, H.; Bardajee, G. R. *Heteroat. Chem.* **2006**, *17*, 136–141.
(332) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Mantellini, F.; Santeusanio, S. *Synlett* **2004**, 549–551.
(333) Bougrin, K.; Loupy, A.; Petit, A.; Daou, B.; Soufiaoui, M. *Tetrahedron* **2001**, *57*, 163–168.
(334) Wang, L. Y.; Zhang, X. G.; Shi, Y. P.; Zhang, Z. X. *Dyes Pigm.* **2004**, *62*, 21–25.
(335) Meziane, M. A. A.; Rahmouni, M.; Bazureau, J. P.; Hamelin, J. *Synthesis* **1998**, 967–969.
(336) Mahesh, R.; Perumal, R. V.; Pandi, P. V. *Pharmazie* **2005**, *60*, 411–414.
(337) Kerneur, G.; Lerestif, J.M.; Bazureau, J. P.; Hamelin, J. *Synthesis* **1997**, 287-&.
(338) Lerestif, J. M.; Perrocheau, J.; Tonnard, F.; Bazureau, J. P.; Hamelin, J. *Tetrahedron* **1995**, *51*, 6757–6774.
(339) Bhattacharjya, G.; Agasti, S. S.; Ramanathan, G. *Arkivoc* **2006**, *10*, 152–161.
(340) Kidwai, M.; Sapra, P.; Bhushan, K. R.; Misra, P. *Synthesis* **2001**, 1509–1512.
(341) Cherouvrier, J. R.; Boissel, J.; Carreaux, F.; Bazureau, J. P. *Green Chem.* **2001**, *3*, 165–169.
(342) Cherouvrier, J. R.; Carreaux, F.; Bazureau, J. P. *Tetrahedron Lett.* **2002**, *43*, 3581–3584.
(343) Cherouvrier, J. R.; Carreaux, F.; Bazureau, J. P. *Tetrahedron Lett.* **2002**, *43*, 8745–8749.
(344) Balalaie, S.; Soleiman-Beigi, M.; Rominger, F. *J. Iran. Chem. Soc.* **2005**, *2*, 319–329.
(345) Uchida, H.; Tanikoshi, H.; Nakamura, S.; Reddy, P. Y.; Toru, T. *Synlett* **2003**, 1117–1120.
(346) Uchida, H.; Shimizu, T.; Reddy, P. Y.; Nakamura, S.; Toru, T. *Synthesis* **2003**, 1236–1240.
(347) Martinez-Palou, R.; de Paz, G.; Marin-Cruz, J.; Zepeda, L. G. *Synlett* **2003**, 1847–1849.
(348) Wu, J.; Sun, X. Y.; Xia, H. G. *Tetrahedron Lett.* **2006**, *47*, 1509–1512.
(349) Gandhi, S.; Bisai, A.; Prasad, B. A. B.; Singh, V. K. *J. Org. Chem.* **2007**, *72*, 2133–2142.
(350) de la Hoz, A.; Diaz-Ortiz, A.; Mateo, M. D.; Moral, M.; Moreno, A.; Elguero, J.; Foces-Foces, C.; Rodriguez, M. L.; Sanchez-Migallon, A. *Tetrahedron* **2006**, *62*, 5868–5874.
(351) Mirkhani, V.; Mohammadpoor-Baltork, I.; Moghadam, M.; Tangestaninejad, S.; Abdollahi-Alibeik, M.; Kargar, H. *Appl. Catal. A: Gen.* **2007**, *325*, 99–104.
(352) Servi, S.; Genc, M. *Synth. Commun.* **2007**, *37*, 3173–3179.
(353) Santagada, V.; Frecentese, F.; Perissutti, E.; Cirillo, D.; Terracciano, S.; Caliendo, G. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4491–4493.
(354) Kaboudin, B.; Saadati, F. *J. Heterocycl. Chem.* **2005**, *42*, 699–701.
(355) Adib, M.; Jahromi, A. H.; Tavoosi, N.; Mahdavi, M.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2006**, *47*, 2965–2967.
(356) Adib, M.; Mahdavi, M.; Mahmoodi, N.; Pirelahi, H.; Bijanzadeh, H. R. *Synlett* **2006**, 1765–1767.
(357) Du, W.; Hagmann, W. K.; Hale, J. J. *Tetrahedron Lett.* **2006**, *47*, 4271–4274.
(358) de Freitas, J. J. R.; Freitas, J. C. R.; da Silva, L. P.; de Freitas, J. R.; Kimura, G. Y. V.; Srivastava, R. M. *Tetrahedron Lett.* **2007**, *48*, 6195–6198.
(359) Du, W.; Truong, Q.; Qi, H. B.; Guo, Y.; Chobanian, H. R.; Hagmann, W. K.; Hale, J. J. *Tetrahedron Lett.* **2007**, *48*, 2231–2235.
(360) Kaboudin, B.; Saadati, F. *Tetrahedron Lett.* **2007**, *48*, 2829–2832.
(361) Díaz-Ortiz, A.; Díez-Barra, E.; De la Hoz, A.; Moreno, A.; Gómez-Escalonilla, M. J.; Loupy, A. *Heterocycles* **1996**, *43*, 1021–1030.
(362) Rostamizadeh, S.; Housaini, S. A. G. *Tetrahedron Lett.* **2004**, *45*, 8753–8756.
(363) Frank, P. V.; Girish, K. S.; Kalluraya, B. *J. Chem. Sci.* **2007**, *119*, 41–46.
(364) Dabiri, M.; Salehi, P.; Baghbanzadeh, M.; Zolfigol, M. A.; Bahramnejad, M. *Synth. Commun.* **2007**, *37*, 1201–1209.
(365) Wang, Z. X.; Qin, H. L. *Green Chem.* **2004**, *6*, 90–92.
(366) Curini, M.; Rosati, O.; Campagna, V.; Montanari, F.; Cravotto, G.; Boccalini, M. *Synlett* **2005**, 2927–2930.
(367) Diaz-Ortiz, A.; de la Hoz, A.; Langa, F. *Green Chem.* **2000**, *2*, 165–172.
(368) Arrieta, A.; Carrillo, J. R.; Cossio, F. P.; Diaz-Ortiz, A.; Gomez-Escalonilla, M. J.; de la Hoz, A.; Langa, F.; Moreno, A. *Tetrahedron* **1998**, *54*, 13167–13180.
(369) Yadav, J. S.; Reddy, B. V. S.; Satheesh, G.; Lakshmi, P. N.; Kumar, S. K.; Kunwar, A. C. *Tetrahedron Lett.* **2004**, *45*, 8587–8590.
(370) Suryakiran, N.; Reddy, T. S.; Latha, K. A.; Prabhakar, P.; Yadagiri, K.; Venkateswarlu, Y. *J. Mol. Catal. A: Chem.* **2006**, *258*, 371–375.
(371) Diaz-Ortiz, A.; de Cozar, A.; Prieto, P.; de la Hoz, A.; Moreno, A. *Tetrahedron Lett.* **2006**, *47*, 8761–8764.
(372) Martins, M. A. P.; Beck, P.; Machado, P.; Brondani, S.; Moura, S.; Zanatta, N.; Bonacorso, H. G.; Flores, A. F. C. *J. Braz. Chem. Soc.* **2006**, *17*, 408–411.
(373) Azarifar, D.; Maleki, B. *Heterocycles* **2005**, *65*, 865–870.
(374) Azarifar, D.; Zolfigol, M. A.; Maleki, B. *Synthesis* **2004**, 1744–1746.
(375) Paul, S.; Gupta, M.; Gupta, R.; Loupy, A. *Tetrahedron Lett.* **2001**, *42*, 3827–3829.
(376) Selvi, S. T.; Nadaraj, V.; Mohan, S.; Sasi, R.; Hema, M. *Bioorg. Med. Chem.* **2006**, *14*, 3896–3903.
(377) Abonia, R.; Rengifo, E.; Quiroga, J.; Insuasty, B.; Cobo, J.; Nogueras, M. *Tetrahedron* **2004**, *60*, 8839–8843.
(378) Zahariev, S.; Guarnaccia, C.; Lamba, D.; Cemazar, M.; Pongor, S. *Tetrahedron Lett.* **2004**, *45*, 9423–9426.
(379) Perez, E. R.; Loupy, A.; Liagre, M.; Plepis, A. M. D.; Cordeiro, P. J. *Tetrahedron* **2003**, *59*, 865–870.
(380) Luo, S. Z.; Zhang, B. L.; Wang, P. G.; Cheng, J. P. *Synth. Commun.* **2003**, *33*, 2989–2994.
(381) Xu, L.; Zhu, D.; Wu, F.; Wang, R. L.; Wan, B. S. *Tetrahedron* **2005**, *61*, 6553–6560.
(382) Rao, V. R.; Srimanth, K. *J. Chem. Res. (S)* **2002**, 420–421.
(383) Manvar, A.; Bochiya, P.; Virsodia, V.; Khunt, R.; Shah, A. *J. Mol. Catal. A: Chem.* **2007**, *275*, 148–152.
(384) Atir, R.; Mallouk, S.; Bougrin, K.; Soufiaoui, M.; Laghzizil, A. *Synth. Commun.* **2006**, *36*, 111–120.
(385) Ben-Alloum, A.; Bakkas, S.; Bougrin, K.; Soufiaoui, M. *New J. Chem.* **1998**, *22*, 809–812.
(386) Syassi, B.; Bougrin, K.; Lamiri, M.; Soufiaoui, M. *New J. Chem.* **1998**, *22*, 1545–1548.
(387) Azarifar, D.; Maleki, B. *J. Heterocycl. Chem.* **2005**, *42*, 157–159.
(388) Kapoor, K. K.; Ganai, B. A.; Kumar, S.; Andotra, C. S. *Synth. Commun.* **2006**, *36*, 2727–2735.
(389) Patel, V. M.; Desai, K. R. *Arkivoc* **2004**, 123–129.
(390) Mojtahedi, M. M.; Jalali, M. R.; Abaee, M. S.; Bolourtchian, M. *Heterocycl. Commun.* **2006**, *12*, 225–228.
(391) Mojtahedi, M. M.; Jalali, M. R.; Bolourtchian, M. *Synth. Commun.* **2006**, *36*, 51–57.
(392) Meddad, N.; Rahmouni, M.; Derdour, A.; Bazureau, J. P.; Hamelin, J. *Synthesis* **2001**, 581–584.
(393) Karale, B. K.; Chavan, V. P.; Mane, A. S.; Hangarge, R. V.; Gill, C. H.; Shingare, M. S. *Synth. Commun.* **2002**, *32*, 497–503.
(394) Xia, M.; Lu, Y. D. *Synth. Commun.* **2006**, *36*, 2389–2399.
(395) Guo, S. B.; Wang, S. X.; Li, J. T. *Synth. Commun.* **2007**, *37*, 2111–2120.
(396) Li, Z.; Yu, J. L.; Yang, J. Y.; Zhu, W.; Zhao, Y. L.; Xing, Y. L.; Wang, X. C. *Phosphorus, Sulfur Silicon Relat. Elem.* **2006**, *181*, 183–190.
(397) Kidwai, M.; Misra, P.; Bhushan, K. R.; Dave, B. *Synth. Commun.* **2000**, *30*, 3031–3040.
(398) Jiang, N.; Li, C. J. *Chem. Commun.* **2004**, 394–395.
(399) Ju, Y. H.; Varma, R. S. *Tetrahedron Lett.* **2005**, *46*, 6011–6014.
(400) Polshettlwar, V.; Varma, R. S. *Tetrahedron Lett.* **2008**, *49*, 397–400.
(401) Adib, M.; Mahdavi, M.; Noghani, M. A.; Mirzaei, P. *Tetrahedron Lett.* **2007**, *48*, 7263–7265.
(402) Lin, M. J.; Sun, C. M. *Synlett* **2004**, 663–666.
(403) Yeh, C. M.; Sun, C. M. *Tetrahedron Lett.* **1999**, *40*, 7247–7250.
(404) Yeh, C. M.; Tung, C. L.; Sun, C. M. *J. Comb. Chem.* **2000**, *2*, 341–348.
(405) Pan, P. C.; Sun, C. M. *Tetrahedron Lett.* **1999**, *40*, 6443–6446.
(406) Zhao, X. Y.; Metz, W. A.; Sieber, F.; Janda, K. D. *Tetrahedron Lett.* **1998**, *39*, 8433–8436.
(407) Xia, M.; Pan, X. J. *Synth. Commun.* **2004**, *34*, 3521–3528.
(408) Lin, M. J.; Sun, C. M. *Tetrahedron Lett.* **2003**, *44*, 8739–8742.
(409) Lee, M. J.; Sun, C. M. *Tetrahedron Lett.* **2004**, *45*, 437–440.
(410) Li, Z.; Yu, J. L.; Ding, R. B.; Wang, Z. Y.; Wang, X. C. *Synth. Commun.* **2004**, *34*, 2981–2986.
(411) Lin, X. F.; Zhang, J.; Cui, S. L.; Wang, Y. G. *Synthesis* **2003**, 1569–1573.
(412) Mathews, C. J.; Smith, P. J.; Welton, T.; White, A. J. P.; Williams, D. J. *Organometallics* **2001**, *20*, 3848–3850.
(413) Xu, L. J.; Chen, W. P.; Xiao, J. L. *Organometallics* **2000**, *19*, 1123–1127.
(414) Carmichael, A. J.; Earle, M. J.; Holbrey, J. D.; McCormac, P. B.; Seddon, K. R. *Org. Lett.* **1999**, *1*, 997–1000.
(415) Howarth, J.; Dallas, A. *Molecules* **2000**, *5*, 851–855.
(416) Zou, G.; Wang, Z. Y.; Zhu, J. R.; Tang, J.; He, M. Y. *J. Mol. Catal. A: Chem.* **2003**, *206*, 193–198.
(417) Xu, J. M.; Wu, W. B.; Qian, C.; Liu, B. K.; Lin, X. F. *Tetrahedron Lett.* **2006**, *47*, 1555–1558.

(418) Attaryan, O. S.; Asratyan, G. V.; Darbinyan, E. G.; Matsoyan, S. G. *Zh. Org. Khim.* **1988**, *24*, 1339–1339.
(419) Timokhin, B. V.; Golubin, A. I.; Vysotskaya, O. V.; Kron, V. A.; Oparina, L. A.; Gusarova, N. K.; Trofimov, B. A. *Chem. Heterocycl. Compd.* **2002**, *38*, 981.
(420) Xu, J. M.; Liu, B. K.; Wu, W. B.; Qian, C.; Wu, Q.; Lin, X. F. *J. Org. Chem.* **2006**, *71*, 3991–3993.
(421) Ranu, B. C.; Banerjee, S. *Org. Lett.* **2005**, *7*, 3049–3052.
(422) Mehnert, C. P.; Dispenziere, N. C.; Cook, R. A. *Chem. Commun.* **2002**, 1610–1611.
(423) Wang, Z. M.; Bao, W. L.; Jiang, Y. *Chem. Commun.* **2005**, 2849–2851.
(424) Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. *J. Org. Chem.* **2003**, *68*, 5381–5383.
(425) Mano, N.; Kim, H. H.; Zhang, Y. C.; Heller, A. *J. Am. Chem. Soc.* **2002**, *124*, 6480–6486.
(426) Savin, G.; Burchard, W.; Luca, C.; Beldie, C. *Macromolecules* **2004**, *37*, 6565–6575.
(427) Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193–6195.
(428) Cooper, G.; Irwin, W. J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 798–803.
(429) Cooper, G.; Irwin, W. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 545–549.
(430) Hayat, S.; Attaur, R.; Choudhary, M. I.; Khan, K. M.; Schumann, W.; Bayer, E. *Tetrahedron* **2001**, *57*, 9951–9957.
(431) Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415–3418.
(432) Shaabani, A.; Rahmati, A.; Aghaaliakbari, B.; Safaei-Ghomi, J. *Synth. Commun.* **2006**, *36*, 65–70.
(433) Frantz, D. E.; Morency, L.; Soheili, A.; Murry, J. A.; Grabowski, E. J. J.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 843–846.
(434) Wasserman, H. H.; Long, Y. O.; Zhang, R.; Parr, J. *Tetrahedron Lett.* **2002**, *43*, 3351–3353.
(435) Sparks, R. B.; Combs, A. P. *Org. Lett.* **2004**, *6*, 2473–2475.
(436) Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. H.; Wang, Y.; Zhao, Z. J.; Lindsley, C. W. *Org. Lett.* **2004**, *6*, 1453–1456.
(437) Zhang, W.; Lu, Y. M. *Org. Lett.* **2003**, *5*, 2555–2558.
(438) Zhang, W.; Nagashima, T.; Lu, Y. M.; Chen, C. H. T. *Tetrahedron Lett.* **2004**, *45*, 4611–4613.
(439) Zhang, W.; Tempest, P. *Tetrahedron Lett.* **2004**, *45*, 6757–6760.
(440) Manku, S.; Curran, D. P. *J. Org. Chem.* **2005**, *70*, 4470–4473.
(441) Zhang, W. *Org. Lett.* **2003**, *5*, 1011–1013.
(442) Katritzky, A. R.; Singh, S. K. *J. Org. Chem.* **2002**, *67*, 9077–9079.
(443) Diez-Gonzalez, S.; Correa, A.; Cavallo, L.; Nolan, S. P. *Chem.—Eur. J.* **2006**, *12*, 7558–7564.
(444) Guezguez, R.; Bougrin, K.; El Akri, K.; Benhida, R. *Tetrahedron Lett.* **2006**, *47*, 4807–4811.
(445) Louerat, F.; Bougrin, K.; Loupy, A.; de Retana, A. M. O.; Pagalday, J.; Palacios, F. *Heterocycles* **1998**, *48*, 161–170.
(446) Roque, D. R.; Neill, J. L.; Antoon, J. W.; Stevens, E. P. *Synthesis* **2005**, 2497–2502.
(447) Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Zunino, E.; Vaccaro, L. *J. Org. Chem.* **2005**, *70*, 6526–6529.
(448) D'Ambrosio, G.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Green Chem.* **2005**, *7*, 874–877.
(449) Vanden Eynde, J. J.; Estiévenart, L.; Van Haverbeke, Y. *Heterocycl. Commun.* **2000**, *6*, 415–420.
(450) Tabatabaee, M.; Ghassemzadeh, M.; Zarabi, B.; Heravi, M. M.; Anary-Abbasinejad, M.; Neumuller, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **2007**, *182*, 677–686.
(451) Kumar, D.; Sekhar, K.; Dhillon, H.; Rao, V. S.; Varma, R. S. *Green Chem.* **2004**, *6*, 156–157.
(452) Mohammadpoor-Baltork, I.; Sadeghi, M. M.; Mallakpour, S. E.; Hajipour, A. R.; Adibi, A. H. *Synth. Commun.* **2002**, *32*, 3445–3448.
(453) Zolfigol, M. A.; Bagherzadeh, M.; Mallakpour, S.; Chehardoli, G.; Kolvari, E.; Choghamarani, A. G.; Koukabi, N. *Catal. Commun.* **2007**, *8*, 256–260.
(454) Mallakpour, S.; Rafiee, Z. *Synlett* **2007**, 1255–1256.
(455) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021.
(456) Wang, Z. X.; Qin, H. L. *Chem. Commun.* **2003**, 2450–2451.
(457) Wijnen, J. W.; Steiner, R. A.; Engberts, J. *Tetrahedron Lett.* **1995**, *36*, 5389–5392.
(458) Pachon, L. D.; van Maarseveen, J. H.; Rothenberg, G. *Adv. Synth. Catal.* **2005**, *347*, 811–815.
(459) Zhao, Y. B.; Yan, Z. Y.; Liang, Y. M. *Tetrahedron Lett.* **2006**, *47*, 1545–1549.
(460) Yan, Z. Y.; Zhao, Y. B.; Fan, M. J.; Liu, W. M.; Liang, Y. M. *Tetrahedron* **2005**, *61*, 9331–9337.
(461) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192–3193.
(462) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210–216.
(463) Díez-González, S.; Correa, A.; Cavallo, L.; Nolan, S. P. *Chem. Eur. J.* **2006**, *12*, 7558–7564.
(464) Zong, Y. X.; Wang, J. K.; Yue, G. R.; Feng, L.; Song, Z. E.; Song, H.; Han, Y. Q. *Tetrahedron Lett.* **2005**, *46*, 5139–5141.
(465) Shou, W. G.; Yang, Y. Y.; Wang, Y. G. *Synthesis* **2005**, 3535–3540.
(466) Kaleta, Z.; Egyed, O.; Soos, T. *Org. Biomol. Chem.* **2005**, *3*, 2228–2230.
(467) Amantini, D.; Beleggia, R.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2004**, *69*, 2896–2898.
(468) Eshghi, H.; Hassankhani, A. *Synth. Commun.* **2005**, *35*, 1115–1120.
(469) Demko, Z. P.; Sharpless, K. B. *J. Org. Chem.* **2001**, *66*, 7945–7950.
(470) Demko, Z. P.; Sharpless, K. B. *Org. Lett.* **2002**, *4*, 2525–2527.
(471) Velazquez, A. M.; Torres, L. A.; Diaz, G.; Ramirez, A.; Hernandez, R.; Santillan, H.; Martinez, L.; Martinez, I.; Diaz-Barriga, S.; Abrego, V.; Balboa, M. A.; Camacho, B.; Lopez-Castanares, R.; Duenas-Gonzalez, A.; Cabrera, G.; Angeles, E. *Arkivoc* **2006**, part ii, 150–161.
(472) Sainz, Y. F.; Raw, S. A.; Taylor, R. J. K. *J. Org. Chem.* **2005**, *70*, 10086–10095.
(473) Diaz-Ortiz, A.; de la Hoz, A.; Prieto, P.; Carrillo, J. R.; Moreno, A.; Neunhoeffer, H. *Synlett* **2001**, 236–237.
(474) Shi, F.; Tu, S. J.; Fang, F.; Li, T. J. *Arkivoc* **2005**, part i, 137–142.
(475) Sharma, U.; Ahmed, S.; Boruah, R. C. *Tetrahedron Lett.* **2000**, *41*, 3493–3495.
(476) Mahesh, R.; Perumal, R. V.; Pandi, P. V. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5179–5181.
(477) Cablewski, T.; Gurr, P. A.; Pajalic, P. J.; Strauss, C. R. *Green Chem.* **2000**, *2*, 25–27.
(478) Quiroga, J.; Portilla, J.; Serrano, H.; Abonia, R.; Insuasty, B.; Nogueras, M.; Cobo, J. *Tetrahedron Lett.* **2007**, *48*, 1987–1990.
(479) Heravi, M. M.; Ghassemzadeh, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2005**, *180*, 347–351.
(480) Varma, R. S.; Kumar, D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1755–1757.
(481) Torchy, S.; Cordonnier, G.; Barbry, D.; Vanden Eynde, J. J. *Molecules* **2002**, *7*, 528–533.
(482) Niknam, K.; Zolfigol, M. A.; Razavian, S. M.; Mohammahpoor-Baltork, I. *J. Heterocycl. Chem.* **2006**, *43*, 199–202.
(483) Diaz-Ortiz, A.; Carrillo, J. R.; Cossio, F. P.; Gomez-Escalonilla, M. J.; de la Hoz, A.; Moreno, A.; Prieto, P. *Tetrahedron* **2000**, *56*, 1569–1577.
(484) Díaz-Ortiz, A.; Carrillo, J. R.; Gómez-Escalonilla, M. J.; De La Hoz, A.; Moreno, A.; Prieto, P. *Synlett* **1998**, 1069–1070.
(485) Quiroga, J.; Cruz, S.; Insuasty, B.; Abonia, R. *Heterocycl. Commun.* **2000**, *6*, 275–282.
(486) Adib, M.; Tahermansouri, H.; Koloogani, S. A.; Mohammadia, B.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2006**, *47*, 5957–5960.
(487) Wang, X. C.; Liu, J.; Li, Z. *J. Chem. Res. (S)* **2005**, 791–792.
(488) Cheng, K.; Lin, L. L.; Chen, S. K.; Feng, X. M. *Tetrahedron* **2005**, *61*, 9594–9599.
(489) Cheng, K.; Zeng, B. Q.; Yu, Z. P.; Gao, B.; Feng, X. M. *Synlett* **2005**, 1018–1020.
(490) Zolfigol, M. A.; Safaiee, M. *Synlett* **2004**, 827–828.
(491) Zolfigol, M. A.; Salehi, P.; Safaiee, M. *Lett. Org. Chem.* **2006**, *3*, 153–156.
(492) Kidwai, M.; Saxena, S.; Mohan, R.; Venkataramanan, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1845–1846.
(493) Suárez, M.; Loupy, A.; Salfrán, E.; Morán, L.; Rolando, E. *Heterocycles* **1999**, *51*, 21–27.
(494) Zolfigol, M. A.; Salehi, P.; Khorramabadi-Zad, A.; Shayegh, M. *J. Mol. Catal. A: Chem.* **2007**, *261*, 88–92.
(495) Eynde, J. J. V.; Labuche, N.; Van Haverbeke, Y. *Synth. Commun.* **1997**, *27*, 3683–3690.
(496) Quiroga, J.; Cisneros, C.; Insuasty, B.; Abonia, R.; Nogueras, M.; Sanchez, A. *Tetrahedron Lett.* **2001**, *42*, 5625–5627.
(497) Quiroga, J.; Portilla, J.; Insuasty, B.; Abonia, R.; Nogueras, M.; Sortino, M.; Zacchino, S. *J. Heterocycl. Chem.* **2005**, *42*, 61–66.
(498) Yadav, L. D. S.; Singh, S. *Synthesis* **2003**, 63–66.
(499) Yadav, L. D. S.; Rai, V. K.; Yadav, S. *Tetrahedron* **2006**, *62*, 5464–5468.
(500) Xiao, D. J.; Wang, L. J.; Feng, X. M. *Synlett* **2005**, 1531–1534.
(501) Panunzio, M.; Lentini, M. A.; Campana, E.; Martelli, G.; Tamanini, E.; Vicennati, P. *Synth. Commun.* **2004**, *34*, 345–359.
(502) Rodriguez, H.; Suarez, M.; Perez, R.; Petit, A.; Loupy, A. *Tetrahedron Lett.* **2003**, *44*, 3709–3712.
(503) Krishnaiah, A.; Narsaiah, B. *J. Fluor. Chem.* **2002**, *113*, 133–137.
(504) Almena, I.; Díaz-Ortiz, A.; Díez-Barra, E.; De La Hoz, A.; Loupy, A. *Chem. Lett.* **1996**, 333–334.
(505) Heber, D.; Stoyanov, E. V. *J. Heterocycl. Chem.* **2000**, *37*, 871–874.

(506) Lopez-Cobenas, A.; Cledera, P.; Sanchez, J. D.; Lopez-Alvarado, P.; Ramos, M. T.; Avendano, C.; Menendez, J. C. *Synthesis* **2005**, 3412–3422.
(507) Lopez-Cobenas, A.; Cledera, P.; Sanchez, J. D.; Perez-Contreras, R.; Lopez-Alvarado, P.; Ramos, M. T.; Avendano, C.; Menendez, J. C. *Synlett* **2005**, 1158–1160.
(508) Jaisinghani, H. G.; Khadilkar, B. M. *Tetrahedron Lett.* **1997**, *38*, 6875–6876.
(509) Yadav, L. D. S.; Singh, S.; Singh, A. *Tetrahedron Lett.* **2002**, *43*, 8551–8553.
(510) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768–1769.
(511) Yu, L. B.; Chen, D. P.; Wang, P. G. *Tetrahedron Lett.* **1996**, *37*, 2169–2172.
(512) Yu, L. B.; Li, J.; Ramirez, J.; Chen, D.; Wang, P. G. *J. Org. Chem.* **1997**, *62*, 903–907.
(513) Akiyama, T.; Takaya, J.; Kagoshima, H. *Tetrahedron Lett.* **1999**, *40*, 7831–7834.
(514) Loncaric, C.; Manabe, K.; Kobayashi, S. *Adv. Synth. Catal.* **2003**, *345*, 475–477.
(515) Loncaric, C.; Manabe, K.; Kobayashi, S. *Chem. Commun.* **2003**, 574–575.
(516) Akiyama, T.; Matsuda, K.; Fuchibe, K. *Synlett* **2002**, 1898–1900.
(517) Yanai, H.; Saito, A.; Taguchi, T. *Tetrahedron* **2005**, *61*, 7087–7093.
(518) Grieco, P. A.; Kaufman, M. D. *J. Org. Chem.* **1999**, *64*, 6041–6048.
(519) Jung, H. H.; Floreancig, P. E. *J. Org. Chem.* **2007**, *72*, 7359–7366.
(520) Smith, C. B.; Raston, C. L.; Sobolev, A. N. *Green Chem.* **2005**, *7*, 650–654.
(521) Porcheddu, A.; Ruda, G. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem.* **2003**, 907–912.
(522) Guo, H. C.; Ding, K. L. *Tetrahedron Lett.* **2003**, *44*, 7103–7106.
(523) Guo, H. C.; Wang, Z.; Ding, K. L. *Synthesis* **2005**, 1061–1068.
(524) Wipf, P.; Hayes, G. B. *Tetrahedron* **1998**, *54*, 6987–6998.
(525) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1921–1940.
(526) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491–2515.
(527) Mo, J.; Xu, L. J.; Xiao, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 751–760.
(528) Ross, J.; Xiao, J. L. *Chem.—Eur. J.* **2003**, *9*, 4900–4906.
(529) Pei, W.; Mo, J.; Xiao, J. L. *J. Organomet. Chem.* **2005**, *690*, 3546–3551.
(530) Subramanyam, C.; Chattarjee, S.; Mallamo, J. P. *Tetrahedron Lett.* **1996**, *37*, 459–462.
(531) Muldoon, M. J.; Gordon, C. M.; Dunkin, I. R. *J. Chem. Soc., Perkin Trans. 2* **2001**, 433–435.
(532) Wasserscheid, P.; Gordon, C. M.; Hilgers, C.; Muldoon, M. J.; Dunkin, I. R. *Chem. Commun.* **2001**, 1186–1187.
(533) Klingshirn, M. A.; Broker, G. A.; Holbrey, J. D.; Shaughnessy, K. H.; Rogers, R. D. *Chem. Commun.* **2002**, 1394–1395.
(534) Zimmermann, J.; Wasserscheid, P.; Tkatchenko, I.; Stutzmann, S. *Chem. Commun.* **2002**, 760–761.
(535) Sliger, M. D.; P'Pool, S. J.; Traylor, R. K.; McNeill, J.; Young, S. H.; Hoffman, N. W.; Klingshirn, M. A.; Rogers, R. D.; Shaughnessy, K. H. *J. Organomet. Chem.* **2005**, *690*, 3540–3545.
(536) Neff, V.; Muller, T. E.; Lercher, J. A. *Chem. Commun.* **2002**, 906–907.
(537) Senn, H. M.; Blochl, P. E.; Togni, A. *J. Am. Chem. Soc.* **2000**, *122*, 4098–4107.
(538) Kitazume, T.; Murata, K.; Okabe, A.; Takahashi, Y.; Yamazaki, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1029–1040.
(539) Hattori, K.; Miyata, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 1151–1152.
(540) Waldmann, H. *Synthesis* **1994**, 535–551.
(541) Zulfiqar, F.; Kitazume, T. *Green Chem.* **2000**, *2*, 137–139.
(542) Shi, M.; Cui, S. C. *New J. Chem.* **2004**, *28*, 1286–1288.
(543) Chen, C. H. T.; Zhang, W. *Org. Lett.* **2003**, *5*, 1015–1017.
(544) Baxendale, I. R.; Ley, S. V. *J. Comb. Chem.* **2005**, *7*, 483–489.
(545) de la Hoz, A.; Blasco, H.; Diaz-Ortiz, A.; Elguero, J.; Foces-Foces, C.; Moreno, A.; Sanchez-Migallon, A.; Valiente, G. *New J. Chem.* **2002**, *26*, 926–932.
(546) Kidemet, D.; Elenkov, I.; Prgomet, V. *Synlett* **2005**, 2531–2533.
(547) Goswami, S.; Jana, S.; Dey, S.; Adak, A. K. *Aust. J. Chem.* **2007**, *60*, 120–123.
(548) Adib, M.; Mahmoodi, N.; Mahdavi, M.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2006**, *47*, 9365–9368.
(549) Gohain, M.; Prajapati, D.; Gogoi, B. J.; Sandhu, J. S. *Synlett* **2004**, 1179–1182.
(550) Eynde, J. J. V.; Hecq, N.; Kataeva, O.; Kappe, C. O. *Tetrahedron* **2001**, *57*, 1785–1791.
(551) Dave, C. G.; Shah, R. D. *Heterocycles* **1999**, *51*, 1819–1826.
(552) Quiroga, J.; Portilla, J.; Abonia, R.; Insuasty, B.; Nogueras, M.; Cobo, J. *Tetrahedron Lett.* **2007**, *48*, 6352–6355.
(553) Prajapati, D.; Gohain, M.; Thakur, A. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3537–3540.
(554) Prasad, M. R.; Prashanth, J.; Shilpa, K.; Kishore, D. P. *Chem. Pharm. Bull.* **2007**, *55*, 557–560.
(555) Prasad, M. R.; Kishore, D. P. *Chem. Pharm. Bull.* **2007**, *55*, 776–779.
(556) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360.
(557) Wipf, P.; Cunningham, A. *Tetrahedron Lett.* **1995**, *36*, 7819–7822.
(558) Oreilly, B. C.; Atwal, K. S. *Heterocycles* **1987**, *26*, 1185–1188.
(559) Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937–6963.
(560) Jiang, Z. D.; Chen, R. F. *Synth. Commun.* **2005**, *35*, 503–509.
(561) Choudhary, V. R.; Tillu, V. H.; Narkhede, V. S.; Borate, H. B.; Wakharkar, R. D. *Catal. Commun.* **2003**, *4*, 449–453.
(562) Mirza-Aghayan, M.; Bolourtchian, M.; Hosseini, M. *Synth. Commun.* **2004**, *34*, 3335–3341.
(563) Yadav, J. S.; Reddy, B. V. S.; Reddy, E. J.; Ramalingam, T. *J. Chem. Res. (S)* **2000**, 354–355.
(564) Bigi, F.; Carloni, S.; Frullanti, B.; Maggi, R.; Sartori, G. *Tetrahedron Lett.* **1999**, *40*, 3465–3468.
(565) Amini, M. M.; Shaabani, A.; Bazgir, A. *Catal. Commun.* **2006**, *7*, 843–847.
(566) Stefani, H. A.; Gatti, P. M. *Synth. Commun.* **2000**, *30*, 2165–2173.
(567) De, S. K.; Gibbs, R. A. *Synthesis* **2005**, 1748–1750.
(568) Dabiri, M.; Arvin-Nezhad, H.; Khavasi, H. R.; Bazgir, A. *Tetrahedron* **2007**, *63*, 1770–1774.
(569) Shaabani, A.; Bazgir, A. *Tetrahedron Lett.* **2004**, *45*, 2575–2577.
(570) Dave, L.C.G.; Agarwal, Y. K.; Thaker, N. H *Indian J. Heterocycl. Chem.* **2005**, *15*, 105–108.
(571) Yadav, L. D. S.; Dubey, S.; Yadav, B. S. *Tetrahedron* **2003**, *59*, 5411–5415.
(572) Heravi, M. M.; Nami, N.; Seifi, N.; Oskooie, H. A.; Hekmatshoar, R. *Phosphorus, Sulfur Silicon Relat. Elem.* **2006**, *181*, 591–599.
(573) Khalafi-Nezhad, A.; Zare, A.; Parhami, A.; Rad, M. N. S.; Nejabat, G. R. *Synth. Commun.* **2006**, *36*, 3549–3562.
(574) Xia, M.; Wang, Y. G. *Synthesis* **2003**, 262–266.
(575) Peng, J. J.; Deng, Y. Q. *Tetrahedron Lett.* **2001**, *42*, 5917–5919.
(576) Zheng, R.; Wang, X.; Xu, H.; Du, J. *Synth. Commun.* **2006**, *36*, 1503–1513.
(577) Ma, Y.; Qian, C. T.; Wang, L. M.; Yang, M. *J. Org. Chem.* **2000**, *65*, 3864–3868.
(578) Rani, V. R.; Srinivas, N.; Kishan, M. R.; Kulkarni, S. J.; Raghavan, K. V. *Green Chem.* **2001**, *3*, 305–306.
(579) Ming, L.; Wei-Si, G.; Li-Rong, W.; Ya-Feng, L.; Hua-Zheng, Y. *J. Mol. Catal. A: Chem.* **2006**, *258*, 133–138.
(580) Dong, F.; Jun, L.; Xinli, Z.; Zhiwen, Y.; Zuliang, L. *J. Mol. Catal. A: Chem.* **2007**, *274*, 208–211.
(581) Legeay, J. C.; Vanden Eynde, J. J.; Bazureau, J. P. *Tetrahedron* **2005**, *61*, 12386–12397.
(582) Bossert, F.; Vater, W. *Med. Res. Rev.* **1989**, *9*, 291–324.
(583) Triggle, D. J.; Langs, D. A.; Janis, R. A. *Med. Res. Rev.* **1989**, *9*, 123–180.
(584) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879–888.
(585) Besson, T.; Brain, C. In *Microwave Assisted Organic Synthesis*; Tierney, J. P., Lidstrom, P., Eds.; Blackwell: Oxford, U.K., 2004.
(586) Larhed, M.; Hallberg, A. *Drug Discovery Today* **2001**, *6*, 406–416.
(587) Blackwell, H. E. *Org. Biomol. Chem.* **2003**, *1*, 1251–1255.
(588) Fraga-Dubreuil, J.; Bazureau, J. P. *Tetrahedron* **2003**, *59*, 6121–6130.
(589) Hakkou, H.; Vanden Eynde, J. J.; Hamelin, J.; Bazureau, J. P. *Tetrahedron* **2004**, *60*, 3745–3753.
(590) Gholap, A. R.; Venkatesan, K.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *Green Chem.* **2004**, *6*, 147–150.
(591) Luche, J. L. *Synthetic Organic Sonochemistry*; Plenum Press: New York, 1998.
(592) Wang, Z. T.; Wang, S. C.; Xu, L. W. *Helv. Chim. Acta* **2005**, *88*, 986–989.
(593) Dondoni, A.; Massi, A. *Tetrahedron Lett.* **2001**, *42*, 7975–7978.
(594) Salehi, P.; Dabir, M.; Zolfigol, M. A.; Fard, M. A. B. *Tetrahedron Lett.* **2003**, *44*, 2889–2891.
(595) Yu, J.; Wang, H. Q. *Synth. Commun.* **2005**, *35*, 3133–3140.
(596) Ravikanth, S.; Reddy, G. V.; Maitraie, D.; Rao, V.; Rao, P. S.; Narsaiah, B. *Synth. Commun.* **2004**, *34*, 4463–4469.
(597) Broom, A. D.; Shim, J. L.; Anderson, G. L. *J. Org. Chem.* **1976**, *41*, 1095–1099.
(598) Cimpeanu, V.; Hardacre, C.; Parvulescu, V. I.; Thompson, J. M. *Green Chem.* **2005**, *7*, 326–332.
(599) Cimpeanu, V.; Parvulescu, V. I.; Amoros, P.; Beltran, D.; Thompson, J. M.; Hardacre, C. *Chem.—Eur. J.* **2004**, *10*, 4640–4646.
(600) Cimpeanu, V.; Parvulescu, A. N.; Parvulescu, V. I.; On, D. T.; Kaliaguine, S.; Thompson, J. M.; Hardacre, C. *J. Catal.* **2005**, *232*, 60–67.
(601) Cimpeanu, V.; Parvulescu, V.; Parvulescu, V. I.; Capron, M.; Grange, P.; Thompson, J. M.; Hardacre, C. *J. Catal.* **2005**, *235*, 184–194.
(602) Wipf, P.; Methot, J. L. *Org. Lett.* **1999**, *1*, 1253–1255.
(603) Studer, A.; Jeger, P.; Wipf, P.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 2917–2924.

(604) Schwinn, D.; Bannwarth, W. *Helv. Chim. Acta* **2002**, *85*, 255–264.
(605) Schwinn, D.; Glatz, H.; Bannwarth, W. *Helv. Chim. Acta* **2003**, *86*, 188–195.
(606) Barthelemy, S.; Schneider, S.; Bannwarth, W. *Tetrahedron Lett.* **2002**, *43*, 807–810.
(607) Mizuno, T.; Iwai, T.; Ishino, Y. *Tetrahedron Lett.* **2004**, *45*, 7073–7075.
(608) Diaz-Ortiz, A.; de la Hoz, A.; Moreno, A.; Sanchez-Migallon, A.; Valiente, G. *Green Chem.* **2002**, *4*, 339–343.
(609) de la Hoz, A.; Diaz-Ortiz, A.; Elguero, J.; Martinez, L. J.; Moreno, A.; Sanchez-Migallon, A. *Tetrahedron* **2001**, *57*, 4397–4403.
(610) Azarifar, D.; Zolfigol, M. A.; Forghaniha, A *Heterocycles* **2004**, *63*, 1897-+.
(611) Kurteva, V. B.; Afonso, C. A. M. *Green Chem.* **2004**, *6*, 183–187.
(612) Diaz-Ortiz, A.; Elguero, J.; de la Hoz, A.; Jimenez, A.; Moreno, A.; Moreno, S.; Sanchez-Migallon, A. *QSAR Comb. Sci.* **2005**, *24*, 649–659.
(613) Dekamin, M. G.; Mallakpour, S.; Ghassemi, M. *J. Chem. Res. (S)* **2005**, 177–179.
(614) Yadav, L. D. S.; Yadav, S.; Rai, V. K. *Green Chem.* **2006**, *8*, 455–458.
(615) Kidwai, M.; Sapra, P.; Bhushan, K. R.; Misra, P. *Synth. Commun.* **2001**, *31*, 1639–1645.
(616) Matikainen, J. K. T.; Elo, H. O. *Microchim. Acta* **2004**, *146*, 49–53.
(617) Butler, R. N.; Fahy, A. M.; Fox, A.; Stephens, J. C.; McArdle, P.; Cunningham, D.; Ryder, A. *J. Org. Chem.* **2006**, *71*, 5679–5687.
(618) Yadav, L. D. S.; Kapoor, R. *Tetrahedron Lett.* **2003**, *44*, 8951–8954.
(619) Heravi, M. M.; Ramezanian, N.; Sadeghi, M. M.; Ghassemzadeh, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2004**, *179*, 1469–1472.
(620) Revankar, G. R.; Matthews, T. R.; Robins, R. K. *J. Med. Chem.* **1975**, *18*, 1253–1255.
(621) Rival, Y.; Grassy, G.; Taudou, A.; Ecalle, R *Eur. J. Med. Chem* **1991**, *26*, 13–18.
(622) Fisher, J. G.; Straley, J. M.; Eastman Kodak Co., 1975.
(623) Buuhoi, N. P.; Xuong, N. D. *Compt. Rend.* **1956**, *243*, 2090–2092.
(624) Rival, Y.; Grassy, G.; Michel, G. *Chem. Pharm. Bull.* **1992**, *40*, 1170–1176.
(625) Sundberg, R. J.; Dahlhausen, D. J.; Manikumar, G.; Mavunkel, B.; Biswas, A.; Srinivasan, V.; King, F.; Waid, P. *J. Heterocycl. Chem.* **1988**, *25*, 129–137.
(626) Xu, D. Q.; Liu, B. Y.; Xu, Z. Y. *Chin. Chem. Lett.* **2003**, *14*, 1002–1004.
(627) Xie, Y. Y. *Synth. Commun.* **2005**, *35*, 1741–1746.
(628) Sridharan, V.; Perumal, S.; Avendano, C.; Menendez, J. C. *Synlett* **2006**, 91–95.
(629) Kabalka, G. W.; Wang, L.; Pagni, R. M. *Tetrahedron* **2001**, *57*, 8017–8028.
(630) Jayashankaran, J.; Manian, R.; Venkatesan, R.; Raghunathan, R. *Tetrahedron* **2005**, *61*, 5595–5598.
(631) Jayashankaran, J.; Manian, R.; Raghunathan, R. *Tetrahedron Lett.* **2004**, *45*, 7303–7305.
(632) Ramesh, E.; Kathiresan, M.; Raghunathan, R. *Tetrahedron Lett.* **2007**, *48*, 1835–1839.
(633) Jaisankar, P.; Srinivasan, P. C. *Synth. Commun.* **2005**, *35*, 923–927.
(634) Sobenina, L. N.; Demenev, A. P.; Mikhaleva, A. I.; Ushakov, I. A.; Vasil'tsov, A. M.; Ivanov, A. V.; Trofimov, B. A. *Tetrahedron Lett.* **2006**, *47*, 7139–7141.
(635) Zhao, J. L.; Liu, L.; Zhang, H. B.; Wu, Y. C.; Wang, D.; Chen, Y. J. *Tetrahedron Lett.* **2006**, *47*, 2511–2514.
(636) Zhao, J. L.; Liu, L.; Zhang, H. B.; Wu, Y. C.; Wang, D.; Chen, Y. J. *Synlett* **2006**, 96–100.
(637) Azizi, N.; Mehrazma, S.; Saidi, M.R. *Can. J. Chem.* **2006**, *84*, 800–803.
(638) Hudlicky, T.; Rinner, U.; Finn, K. J.; Ghiviriga, I. *J. Org. Chem.* **2005**, *70*, 3490–3499.
(639) Dandia, A.; Singh, R.; Arya, K. *Phosphorus, Sulfur Silicon Relat. Elem.* **2004**, *179*, 551–564.
(640) Dandia, A.; Singh, R.; Sarawgi, P.; Khaturia, S. *Chin. J. Chem.* **2006**, *24*, 950–954.
(641) Dandia, A.; Arya, K.; Khaturia, S.; Yadav, P. *Arkivoc* **2005**, 80–88.
(642) Shanthi, G.; Subbulakshmi, G.; Perumal, P. T. *Tetrahedron* **2007**, *63*, 2057–2063.
(643) Firouzabadi, H.; Iranpoor, N.; Jafarpour, M.; Ghaderi, A. *J. Mol. Catal. A: Chem.* **2006**, *252*, 150–155.
(644) Firouzabadi, H.; Iranpoor, N.; Jafarpour, M.; Ghaderi, A. *J. Mol. Catal. A: Chem.* **2006**, *253*, 249–251.
(645) Ballini, R.; Clemente, R. R.; Palmieri, A.; Petrini, M. *Adv. Synth. Catal.* **2006**, *348*, 191–196.
(646) Bartoli, G.; Bosco, M.; Giuli, S.; Giuliani, A.; Lucarelli, L.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2005**, *70*, 1941–1944.
(647) Bartoli, G.; Bartolacci, M.; Bosco, M.; Foglia, G.; Giuliani, A.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2003**, *68*, 4594–4597.
(648) An, L. T.; Zou, J. P.; Zhang, L. L.; Zhang, Y. *Tetrahedron Lett.* **2007**, *48*, 4297–4300.
(649) Deb, M. L.; Bhuyan, P. J. *Tetrahedron Lett.* **2007**, *48*, 2159–2163.
(650) Chakrabarty, M.; Basak, R.; Ghosh, N. *Tetrahedron Lett.* **2001**, *42*, 3913–3915.
(651) Chakrabarty, M.; Basak, R.; Ghosh, N.; Harigaya, Y. *Tetrahedron* **2004**, *60*, 1941–1949.
(652) Banik, B. K.; Fernandez, M.; Alvarez, C. *Tetrahedron Lett.* **2005**, *46*, 2479–2482.
(653) Ji, S. J.; Wang, S. Y.; Zhang, Y.; Loh, T. P. *Tetrahedron* **2004**, *60*, 2051–2055.
(654) An, L. T.; Qing, F. Q.; Zou, J. P.; Lu, X. H.; Zhang, L. L. *Chin. J. Chem.* **2007**, *25*, 822–827.
(655) Pore, D. M.; Desai, U. V.; Thopate, T. S.; Wadgaonkar, P. P. *Arkivoc* **2006**, *12*, 75–80.
(656) Kamble, V. T.; Bandgar, B. P.; Bavikar, S. N. *Chin. J. Chem.* **2007**, *25*, 13–15.
(657) Azizian, J.; Teimouri, F.; Mohammadizadeh, M. R. *Catal. Commun.* **2007**, *8*, 1117–1121.
(658) Hosseini-Sarvari, M. *Acta Chim. Slov.* **2007**, *54*, 354–359.
(659) Dabiri, M.; Salehi, P.; Baghbanzadeh, M.; Vakilzadeh, Y.; Kiani, S. *Monatsh. Chem.* **2007**, *138*, 595–597.
(660) Xia, M.; Wang, S. H.; Yuan, W. B. *Synth. Commun.* **2004**, *34*, 3175–3182.
(661) Chakrabarty, M.; Mukherjee, R.; Mukherji, A.; Arima, S.; Harigaya, Y. *Heterocycles* **2006**, *68*, 1659–1668.
(662) Mehrazma, S.; Azizi, N.; Saidi, M. R. *Lett. Org. Chem.* **2006**, *3*, 161–164.
(663) Chakrabarty, M.; Ghosh, N.; Basak, R.; Harigaya, Y. *Tetrahedron Lett.* **2002**, *43*, 4075–4078.
(664) Chakrabarty, M.; Sarkar, S. *Tetrahedron Lett.* **2002**, *43*, 1351–1353.
(665) Chakrabarty, M.; Sarkar, S.; Linden, A.; Stein, B. K. *Synth. Commun.* **2004**, *34*, 1801–1810.
(666) Dinica, R. M.; Druta, II; Pettinari, C. *Synlett* **2000**, 1013–1015.
(667) Pal, B.; Jaisankar, P.; Giri, V. S. *Synth. Commun.* **2003**, *33*, 2339–2348.
(668) Hatamjafari, F. *Synth. Commun.* **2006**, *36*, 3563–3570.
(669) Kremsner, J. M.; Kappe, C. O. *Eur. J. Org. Chem.* **2005**, *367*, 2–3679.
(670) Zhang, H. B.; Liu, L.; Chen, Y. J.; Wang, D.; Li, C. J. *Eur. J. Org. Chem.* **2006**, 869–873.
(671) Yan, B.; Liu, Y. H. *Org. Lett.* **2007**, *9*, 4323–4326.
(672) Yeh, W. B.; Lin, M. J.; Sun, C. M. *Tetrahedron Lett.* **2003**, *44*, 4923–4926.
(673) Chen, Z. X.; Yue, G. Z.; Lu, C. F.; Yang, G. C. *Synlett* **2004**, 1231–1234.
(674) Yue, G. H.; Wan, Y. D.; Song, S. J.; Yang, G. C.; Chen, Z. X. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 453–458.
(675) Nunomoto, S.; Kawakami, Y.; Yamashita, Y.; Takeuchi, H.; Eguchi, S. *J. Chem. Soc., Perkin Trans. 1* **1990**, 111–114.
(676) Earle, M. J.; McCormac, P. B.; Seddon, K. R. *Chem. Commun.* **1998**, 2245–2246.
(677) Robinson, B *Chem. Rev* **1963**, *63*, 373–401.
(678) Xu, D.-Q.; Yang, W.-L.; Luo, S.-P.; Wang, B.-T.; Wu, J.; Xu, Z.-Y. *Eur. J. Org. Chem.* **2007**, 1007–1012.
(679) Rebeiro, G. L.; Khadilkar, B. M. *Synthesis* **2001**, 370–372.
(680) Fisher, E. *Liebigs Ann. Chem.* **1886**, *236*, 133.
(681) Kissman, H. M.; Farnsworth, D. W.; Witkop, B. *J. Am. Chem. Soc.* **1952**, *74*, 3948–3949.
(682) Baccolini, G.; Todesco, P. E. *J. Chem. Soc., Chem. Commun.* **1981**, 563–564.
(683) Brown, D. W.; Mahon, M. F.; Ninan, A.; Sainsbury, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2329–2336.
(684) Morales, R. C.; Tambyrajah, V.; Jenkins, P. R.; Davies, D. L.; Abbott, A. P. *Chem. Commun.* **2004**, 158–159.
(685) Baudoux, J.; Salit, A. F.; Cahard, D.; Plaquevent, J. C. *Tetrahedron Lett.* **2002**, *43*, 6573–6574.
(686) Cahard, D.; Audouard, C.; Plaquevent, J. C.; Roques, N. *Org. Lett.* **2000**, *2*, 3699–3701.
(687) Mohar, B.; Baudoux, M.; Plaquevent, J. C.; Cahard, D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4214–4216.
(688) Yeung, K. S.; Farkas, M. E.; Qiu, Z. L.; Yang, Z. *Tetrahedron Lett.* **2002**, *43*, 5793–5795.
(689) Ji, S. J.; Wang, S. Y. *Synlett* **2003**, 2074–2076.
(690) Gu, D. G.; Ji, S. J.; Jiang, Z. Q.; Zhou, M. F.; Loh, T. P. *Synlett* **2005**, 959–962.
(691) Mi, X. L.; Luo, S. Z.; He, J. Q.; Cheng, J. P. *Tetrahedron Lett.* **2004**, *45*, 4567–4570.
(692) Chen, D. P.; Yu, L. B.; Wang, P. G. *Tetrahedron Lett.* **1996**, *37*, 4467–4470.

(693) Yadav, J. S.; Reddy, B. V. S.; Baishya, G.; Reddy, K. V.; Narsaiah, A. V. *Tetrahedron* **2005**, *61*, 9541–9544.
(694) Curran, D. P.; Hadida, S.; Kim, S. Y.; Luo, Z. Y. *J. Am. Chem. Soc.* **1999**, *121*, 6607–6615.
(695) Crich, D.; Barba, G. R. *Org. Lett.* **2000**, *2*, 989–991.
(696) Lin, M. J.; Zhang, W.; Sun, C. M. *J. Comb. Chem.* **2007**, *9*, 951–958.
(697) Kasahara, T.; Kondo, Y. *Chem. Commun.* **2006**, 891–893.
(698) Naka, H.; Akagi, Y.; Yamada, K.; Imahori, T.; Kasahara, T.; Kondo, Y. *Eur. J. Org. Chem.* **2007**, 4635–4637.
(699) Jia, C. S.; Zhang, Z.; Tu, S. J.; Wang, G. W. *Org. Biomol. Chem.* **2006**, *4*, 104–110.
(700) Agrawal, Y.K.; Joshipura, H. M *Indian J. Chem., Sect B: Org. Chem. Incl. Med. Chem* **2005**, *44*, 1649–1652.
(701) Shaabani, A.; Soleimani, E.; Badri, Z. *Monatsh. Chem.* **2006**, *137*, 181–184.
(702) Zolfigol, M. A.; Salehi, P.; Shiri, M.; Rastegar, T. F.; Ghaderi, A. *J. Iran. Chem. Soc.* **2008**, *5*, 490–497.
(703) Dabiri, M.; Azimi, S. C.; Bazgir, A. *Monatsh. Chem.* **2007**, *138*, 659–661.
(704) Shaabani, A.; Soleimani, E.; Badri, Z. *Synth. Commun.* **2007**, *37*, 629–635.
(705) Song, S. J.; Cho, S. J.; Park, D. K.; Kwon, T. W.; Jenekhe, S. A. *Tetrahedron Lett.* **2003**, *44*, 255–257.
(706) Taguchi, K.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2005**, *46*, 4539–4542.
(707) Martinez, R.; Ramon, D. J.; Yus, M. *Eur. J. Org. Chem.* **2007**, 1599–1605.
(708) Yadav, J. S.; Reddy, B. V. S.; Rao, R. S.; Naveenkumar, V.; Nagaiah, K. *Synthesis* **2003**, 1610–1614.
(709) Zhang, J. M.; Yang, W.; Song, L. P.; Cai, M.; Zhu, S. Z. *Tetrahedron Lett.* **2004**, *45*, 5771–5773.
(710) Ranu, B. C.; Hajra, A.; Dey, S. S.; Jana, U. *Tetrahedron* **2003**, *59*, 813–819.
(711) Ranu, B. C.; Hajra, A.; Jana, U. *Tetrahedron Lett.* **2000**, *41*, 531–533.
(712) Kidwai, M.; Bhushan, K. R.; Sapra, P.; Saxena, R. K.; Gupta, R. *Bioorg. Med. Chem.* **2000**, *8*, 69–72.
(713) Chaudhuri, M. K.; Hussain, S. *J. Chem. Sci.* **2006**, *118*, 199–202.
(714) Chaitanya, T. K.; Nagarajan, R. *Tetrahedron Lett.* **2007**, *48*, 2489–2492.
(715) Musiol, R.; Podeszwa, B.; Finster, J.; Niedbala, H.; Polanski, J. *Monatsh. Chem.* **2006**, *137*, 1211–1217.
(716) Devi, L.; Baruah, B.; Bhuyan, P. J. *Synlett* **2006**, 2593–2596.
(717) Loghmani-Khouzani, H.; Sadeghi, M. M.; Safari, J. *Molecules* **2002**, *7*, 135–139.
(718) Mortoni, A.; Martinelli, M.; Piarulli, U.; Regalia, N.; Gagliardi, S. *Tetrahedron Lett.* **2004**, *45*, 6623–6627.
(719) Veverkova, E.; Noskova, M.; Toma, S. *Synth. Commun.* **2002**, *32*, 729–733.
(720) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A. *Green Chem.* **2005**, *7*, 825–827.
(721) Tu, S.; Wei, Q.; Ma, H.; Shi, D.; Gao, Y.; Cui, G. *Synth. Commun.* **2001**, *31*, 2657–2661.
(722) Yadav, J. S.; Reddy, B. V. S.; Premalatha, K.; Murty, M. S. R. *J. Mol. Catal. A: Chem.* **2007**, *271*, 161–163.
(723) Charris, J.; Barazarte, A.; Dominguez, J.; Gamboa, N. *J. Chem. Res. (S)* **2005**, 27–28.
(724) Cernuchova, P.; Vo-Thanh, G.; Milata, V.; Loupy, A. *Heterocycles* **2004**, *64*, 177–191.
(725) Kidwai, M.; Misra, P.; Dave, B.; Bhushan, K. R.; Saxena, R. K.; Singh, M. *Monatsh. Chem.* **2000**, *131*, 1207–1212.
(726) Lange, J. H. M.; Verveer, P. C.; Osnabrug, S. J. M.; Visser, G. M. *Tetrahedron Lett.* **2001**, *42*, 1367–1369.
(727) Varma, R. S.; Saini, R. K. *Synlett* **1997**, *1997*, 857–858.
(728) Kumar, K. H.; Muralidharan, D.; Perumal, P. T. *Synthesis* **2004**, 63–68.
(729) Ahmed, N.; van Lier, J. E. *Tetrahedron Lett.* **2006**, *47*, 2725–2729.
(730) Ahmed, N.; van Lier, J. E. *Tetrahedron Lett.* **2007**, *48*, 13–15.
(731) Jia, C. S.; Dong, Y. W.; Tu, S. J.; Wang, G. W. *Tetrahedron* **2007**, *63*, 892–897.
(732) Yadav, L. D. S.; Kapoor, R. *Synlett* **2005**, 3055–3058.
(733) Yadav, L. D. S.; Rai, V. K. *Tetrahedron Lett.* **2006**, *47*, 395–397.
(734) Wang, G. W.; Jia, C. S.; Dong, Y. W. *Tetrahedron Lett.* **2006**, *47*, 1059–1063.
(735) Zolfigol, M. A.; Salehi, P.; Ghaderi, A.; Shiri, M. *Catal. Commun.* **2007**, *8*, 1214–1218.
(736) Zolfigol, M. A.; Salehi, P.; Ghaderi, A.; Shiri, M.; Tanbakouchian, Z. *J. Mol. Catal. A: Chem.* **2006**, *259*, 253–258.
(737) Chen, L.; Li, Z. G.; Li, C. J. *Synlett* **2003**, 732–734.
(738) Zhang, J. H.; Li, C. J. *J. Org. Chem.* **2002**, *67*, 3969–3971.
(739) Li, Z. G.; Zhang, J. H.; Li, C. J. *Tetrahedron Lett.* **2003**, *44*, 153–156.
(740) Chen, L.; Li, C. J. *Green Chem.* **2003**, *5*, 627–629.
(741) Yadav, J. S.; Reddy, B. V. S.; Srinivas, M.; Padmavani, B. *Tetrahedron* **2004**, *60*, 3261–3266.
(742) Saito, A.; Numaguchi, J.; Hanzawa, Y. *Tetrahedron Lett.* **2007**, *48*, 835–839.
(743) Saito, A.; Takayama, M.; Yamazaki, A.; Numaguchi, J.; Hanzawa, Y. *Tetrahedron* **2007**, *63*, 4039–4047.
(744) Saha, B.; Sharma, S.; Sawant, D.; Kundu, B. *Tetrahedron Lett.* **2007**, *48*, 1379–1383.
(745) Wang, Y. G.; Lin, X. F.; Cui, S. J. *Synlett* **2004**, 1175–1178.
(746) Xu, L. K.; Lam, K. H.; Ji, J. X.; Wu, J.; Fan, Q. H.; Lo, W. H.; Chan, A. S. C. *Chem. Commun.* **2005**, 1390–1392.
(747) Lam, K. H.; Xu, L. J.; Feng, L. C.; Fan, Q. H.; Lam, F. L.; Lo, W. H.; Chan, A. S. C. *Adv. Synth. Catal.* **2005**, *347*, 1755–1758.
(748) Blettner, C. G.; Konig, W. A.; Ruhter, G.; Stenzel, W.; Schotten, T. *Synlett* **1999**, 307–310.
(749) Fehnel, E.A. *J. Org. Chem* **1966**, *31*, 2899–2902.
(750) Friedlaender, P. *Ber.* **1882**, *15*, 2572–2575.
(751) Zhang, X. Y.; Fan, X. S.; Wang, J. J.; Li, Y. Z. *J. Chin. Chem. Soc.* **2004**, *51*, 1339–1342.
(752) Dabiri, M.; Salehi, P.; Baghbanzadeh, M.; Nikcheh, M. S. *Tetrahedron Lett.* **2008**, *49*, 5366–5368.
(753) Johnson, J. V.; Rauckman, B. S.; Baccanari, D. P.; Roth, B. *J. Med. Chem.* **1989**, *32*, 1942–1949.
(754) Yamada, N.; Kadowaki, S.; Takahashi, K.; Umezu, K. *Biochem. Pharmacol.* **1992**, *44*, 1211–1213.
(755) Baudelle, R.; Melnyk, P.; Deprez, B.; Tartar, A. *Tetrahedron* **1998**, *54*, 4125–4140.
(756) Crousse, B.; Begue, J. P.; Bonnet-Delpon, D. *Tetrahedron Lett.* **1998**, *39*, 5765–5768.
(757) Yadav, J. S.; Reddy, B. V. S.; Reddy, J. S. S.; Rao, R. S. *Tetrahedron* **2003**, *59*, 1599–1604.
(758) Wang, X.-S.; Zhang, M.-M.; Jiang, H.; Yao, C.-S.; Tu, S.-J. *Tetrahedron* **2007**, *63*, 4439–4449.
(759) Ma, Y.; Qian, C. T.; Xie, M. H.; Sun, J. *J. Org. Chem.* **1999**, *64*, 6462–6467.
(760) Yadav, J. S.; Reddy, B. V. S.; Raj, K. S.; Prasad, A. R. *Tetrahedron* **2003**, *59*, 1805–1809.
(761) Gray, N. M.; Dappen, M. S.; Cheng, B. K.; Cordi, A. A.; Biesterfeldt, J. P.; Hood, W. F.; Monahan, J. B. *J. Med. Chem.* **1991**, *34*, 1283–1292.
(762) Shi, D. Q.; Ni, S. N.; Yang, F.; Shi, J. W.; Dou, G. L.; Li, X. Y.; Wang, X. S. *J. Heterocycl. Chem.* **2008**, *45*, 653–660.
(763) McAllister, L. A.; McCormick, R. A.; Brand, S.; Procter, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 452–455.
(764) McCormick, R. A.; James, K. M.; Willetts, N.; Procter, D. J. *QSAR Comb. Sci.* **2006**, *25*, 709–712.
(765) Luo, Z. Y.; Williams, J.; Read, R. W.; Curran, D. P. *J. Org. Chem.* **2001**, *66*, 4261–4266.
(766) Curran, D. P.; Amatore, M.; Guthrie, D.; Campbell, M.; Go, E.; Luo, Z. Y. *J. Org. Chem.* **2003**, *68*, 4643–4647.
(767) Zhang, W.; Lu, Y. M.; Nagashima, T. *J. Comb. Chem.* **2005**, *7*, 893–897.
(768) Zhang, W.; Luo, Z. Y.; Chen, C. H. T.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 10443–10450.
(769) Kumar, V.; Mohan, C.; Gupta, M.; Mahajan, M. P. *Tetrahedron* **2005**, *61*, 3533–3538.
(770) Seijas, J. A.; Vazquez-Tato, M. P.; Martinez, M. M. *Tetrahedron Lett.* **2000**, *41*, 2215–2217.
(771) Kurteva, V. B.; Zlatanova, V. N.; Dimitrov, V. D. *Arkivoc* **2006**, 46–56.
(772) Ganai, B. A.; Koul, S.; Razdan, T. K.; Andotra, C. S. *Synth. Commun.* **2004**, *34*, 1819–1823.
(773) Wang, L. M.; Xia, J. J.; Qin, F.; Qian, C. T.; Sun, J. *Synthesis* **2003**, 1241–1247.
(774) Chari, M. A.; Shobha, D.; Mukkanti, K. *Catal. Commun.* **2006**, *7*, 787–790.
(775) Narasimhulu, M.; Mahesh, K. C.; Reddy, T. S.; Rajesh, K.; Venkateswarlu, Y. *Tetrahedron Lett.* **2006**, *47*, 4381–4383.
(776) Lingaiah, B. V.; Ezikiel, G.; Yakaiah, T.; Reddy, G. V.; Rao, P. S. *Synlett* **2006**, 2507–2509.
(777) Alexandre, F.-R.; Berecibar, A.; Besson, T. *Tetrahedron Lett.* **2002**, *43*, 3911–3913.
(778) Alexandre, F.-R.; Berecibar, A.; Wrigglesworth, R.; Besson, T. *Tetrahedron* **2003**, *59*, 1413–1419.
(779) Rad-Moghadam, K.; Mamghani, M.; Samavi, L. *Synth. Commun.* **2006**, *36*, 2245–2252.
(780) Salehi, P.; Zolfigol, M. A.; Shirini, F.; Baghbanzadeh, M. *Curr. Org. Chem.* **2006**, *10*, 2171–2189.
(781) Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Baghbanzadeh, M. *Tetrahedron Lett.* **2005**, *46*, 7051–7053.
(782) Rad-Moghadam, K.; Mohseni, M. *J. Chem. Res. (S)* **2003**, 487–488.

(783) Dabiri, M.; Salehi, P.; Mohammadi, A. A.; Baghbanzadeh, M. *Synth. Commun.* **2005**, *35*, 279–287.
(784) Montazeri, N.; Rad-Moghadam, K. *Phosphorus, Sulfur Silicon Relat. Elem.* **2004**, *179*, 2533–2536.
(785) Kidwai, M.; Rastogi, S.; Mohan, R.; Ruby, *Croat. Chem. Acta* **2003**, *76*, 365–369.
(786) Dandia, A.; Singh, R.; Sarawgi, P. *J. Fluor. Chem.* **2005**, *126*, 307–312.
(787) Yadav, J. S.; Reddy, B. V. S. *Tetrahedron Lett.* **2002**, *43*, 1905–1907.
(788) Cledera, P.; Sanchez, J. D.; Caballero, E.; Avendano, C.; Ramos, M. T.; Menendez, J. C. *Synlett* **2004**, 803–806.
(789) Juncai, F.; Yang, L.; Qinghua, M.; Bin, L. *Synth. Commun.* **1998**, *28*, 193–196.
(790) Mohsenzadeh, F.; Aghapoor, K.; Darabi, H. R. *J. Braz. Chem. Soc.* **2007**, *18*, 297–303.
(791) Azizian, J.; Mohammadizadeh, M. R.; Karimi, N.; Kazemizadeh, Z.; Mohammadi, A. A.; Karimi, A. R. *Heteroat. Chem.* **2005**, *16*, 549–552.
(792) Heravi, M. M.; Nami, N.; Oskooie, H. A.; Hekmatshoar, R. *Phosphorus, Sulfur Silicon Relat. Elem.* **2005**, *180*, 1873–1878.
(793) Wang, L. M.; Liu, J. J.; Tian, H.; Qian, C. T. *Synth. Commun.* **2004**, *34*, 1349–1357.
(794) Vazquez, E.; de la Hoz, A.; Elander, N.; Moreno, A.; Stone-Elander, S. *Heterocycles* **2001**, *55*, 109–113.
(795) Habibi, D.; Marvi, O. *Catal. Commun.* **2007**, *8*, 127–130.
(796) Habibi, D.; Mahmoudi, N.; Marvi, O. *Synth. Commun.* **2007**, *37*, 3165–3171.
(797) Dabiri, M.; Salehi, P.; Baghbanzadeh, M.; Zolfigol, M. A.; Agheb, M.; Heydari, S. *Catal. Commun.* **2008**, *9*, 785–788.
(798) Butler, R. N.; Cunningham, W. J.; Coyne, A. G.; Burke, L. A. *J. Am. Chem. Soc.* **2004**, *126*, 11923–11929.
(799) Butler, R. N.; Coyne, A. G.; Cunningham, W. J.; Burke, L. A. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1807–1815.
(800) Butler, R. N.; Coyne, A. G.; Cunningham, W. J.; Moloney, E. M.; Burke, L. A. *Helv. Chim. Acta* **2005**, *88*, 1611–1629.
(801) Butler, R. N.; Coyne, A. G.; Moloney, E. M. *Tetrahedron Lett.* **2007**, *48*, 3501–3503.
(802) Schultz, H. *Benzodiazepines*; Springer: Heidelberg, Germany, 1982.
(803) Yadav, J. S.; Reddy, B. V. S.; Praveenkumar, S.; Nagaiah, K. *Synthesis* **2005**, 480–484.
(804) Xia, M.; Lu, Y. D. *Heteroat. Chem.* **2007**, *18*, 354–358.
(805) Li, Z. J.; Sun, Y. J.; Ren, X. H.; Li, W. S.; Shi, Y. H.; Ouyang, P. K. *Synth. Commun.* **2007**, *37*, 1609–1615.
(806) Pozarentzi, M.; Stephanidou-Stephanatou, J.; Tsoleridis, C. A. *Tetrahedron Lett.* **2002**, *43*, 1755–1758.
(807) Ganai, B. A.; Kumar, S.; Andotra, C. S.; Kapoor, K. K. *Synth. Commun.* **2006**, *36*, 803–807.
(808) Kidwai, M.; Sapra, P.; Misra, P.; Saxena, R. K.; Singh, M. *Bioorg. Med. Chem.* **2001**, *9*, 217–220.
(809) Raghavendra, M.; Naik, H. S. B.; Naik, T.; Sherigara, B. S. *Phosphorus, Sulfur Silicon Relat. Elem.* **2007**, *182*, 1823–1831.
(810) Dandia, A.; Singh, R.; Khaturia, S. *J. Fluor. Chem.* **2007**, *128*, 524–529.
(811) Palimkar, S. S.; Lahoti, R. J.; Srinivasan, K. V. *Green Chem.* **2007**, *9*, 146–152.
(812) Declerck, V.; Ribiere, P.; Nedellec, Y.; Allouchi, H.; Martinez, J.; Lamaty, F. *Eur. J. Org. Chem.* **2007**, 201–208.
(813) Ribiere, P.; Declerck, V.; Nedellec, Y.; Yadav-Bhatnagar, N.; Martinez, J.; Lamaty, F. *Tetrahedron* **2006**, *62*, 10456–10466.
(814) Nouvet, A.; Binard, M.; Lamaty, F.; Martinez, J.; Lazaro, R. *Tetrahedron* **1999**, *55*, 4685–4698.
(815) Jarikote, D. V.; Siddiqui, S. A.; Rajagopal, R.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *Tetrahedron Lett.* **2003**, *44*, 1835–1838.
(816) Ried, W.; Stahlhofen, P. *Chem. Ber. Recl.* **1957**, *90*, 815–824.
(817) Ried, W.; Torinus, E. *Chem. Ber. Recl.* **1959**, *92*, 2902–2916.
(818) Morales, H. R.; Bulbarela, A.; Contreras, R. *Heterocycles* **1986**, *24*, 135–139.
(819) Jung, D. I.; Choi, T. W.; Kim, Y. Y.; Kim, I. S.; Park, Y. M.; Lee, Y. G.; Jung, D. H. *Synth. Commun.* **1999**, *29*, 1941–1951.
(820) Herbert, J. A. L.; Suschitzky, H. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2657–2661.
(821) Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Tetrahedron Lett.* **2001**, *42*, 3193–3195.
(822) Kaboudin, B.; Navaee, K. *Heterocycles* **2001**, *55*, 1443–1446.
(823) Avent, A. G.; Chaloner, P. A.; Day, M. P.; Seddon, K. R.; Welton, T. *J. Chem. Soc., Dalton Trans.* **1994**, 3405–3413.
(824) Howarth, J.; Hanlon, K.; Fayne, D.; McCormac, P. *Tetrahedron Lett.* **1997**, *38*, 3097–3100.
(825) Gui, J.; Deng, Y.; Hu, Z.; Sun, Z. *Tetrahedron Lett.* **2004**, *45*, 2681–2683.
(826) Kamimura, A.; Yamamoto, S. *Org. Lett.* **2007**, *9*, 2533–2535.
(827) Zhang, W.; Lu, Y.; Chen, C. H. T.; Curran, D. P.; Geib, S. *Eur. J. Org. Chem.* **2006**, 2055–2059.
(828) Zhang, W.; Lu, Y. M.; Chen, C. H. T.; Zeng, L.; Kassel, D. B. *J. Comb. Chem.* **2006**, *8*, 687–695.
(829) Zhang, W.; Williams, J. P.; Lu, Y. M.; Nagashima, T.; Chu, Q. L. *Tetrahedron Lett.* **2007**, *48*, 563–565.

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