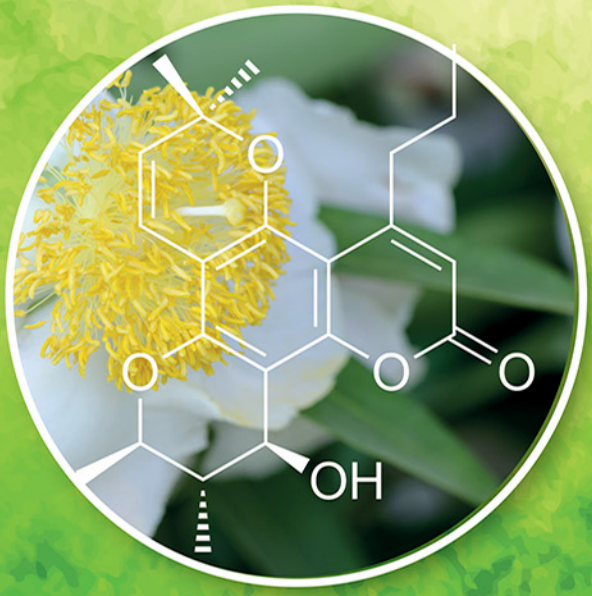
Advances in **Green and Sustainable Chemistry**

Second Edition



Green Synthetic Approaches for Biologically Relevant Heterocycles

Volume 2: Green Catalytic Systems and Solvents

Edited by
Goutam Brahmachari

ELSEVIER

Advances in Green and Sustainable Chemistry

Green Synthetic Approaches for Biologically Relevant Heterocycles

Volume 2: Green Catalytic Systems and Solvents

Second Edition

Edited by

Goutam Brahmachari
Laboratory of Natural Products & Organic Synthesis, Department of Chemistry, Visva-Bharati (A Central University), Santiniketan, India

ELSEVIER

Contents

Chapter 14

Green synthetic approaches for medium ring–sized heterocycles of biological and pharmaceutical interest

Saikat Chaudhuri, Amrita Ghosh and Shital K Chattopadhyay
Department of Chemistry, University of Kalyani, Kalyani, India

14.1 Introduction

Heterocyclic compounds constitute an important class of compounds because of their prevalence in natural products of marine and terrestrial origin [1] and pharmaceutical compounds [1,2]. Many of the approved drugs contain heterocyclic ring system as active pharmacophoric part. The wide variety of heterocyclic ring systems offers a unique advantage in the arena of pharmaceuticals as small lead compounds in drug design. Among different kinds of heterocyclic ring systems, nitrogen heterocyclic compounds are more abundant in nature as part structural unit of important bioactive compounds such as antibiotics, vitamins, and hormones. They are also prevalent among herbicides, fungicides, and other application-oriented molecules. It is gratifying to note that heterocyclic compounds constitute nearly 50% of known organic compounds and nearly 90% of active pharmaceuticals. Majority of these heterocyclic drugs contain small ring structures ranging from 3 to 6. However, medium ring–sized heterocyclic compounds (7–9 members) are gaining quick recognition as important heterocyclic motifs of biological relevance in drug design over the last few decades. In particular, ring systems such as oxepine, oxocin, azepine, azocine, diazepin, dioxepine, oxazepine, thiazepine, and their benzo-fused analogs are found in compounds associated with a wide range of physiological activities. It is recorded that >2000 oxepine structures and more that 350 azepine structures are associated with pharmacological activities. Similarly, medium ring–sized systems containing more than two hetero atoms of one or more kinds have also appeared as compounds of considerable

Green Synthetic Approaches for Biologically Relevant Heterocycles.
DOI: https://doi.org/10.1016/B978-0-12-820792-5.00004-4

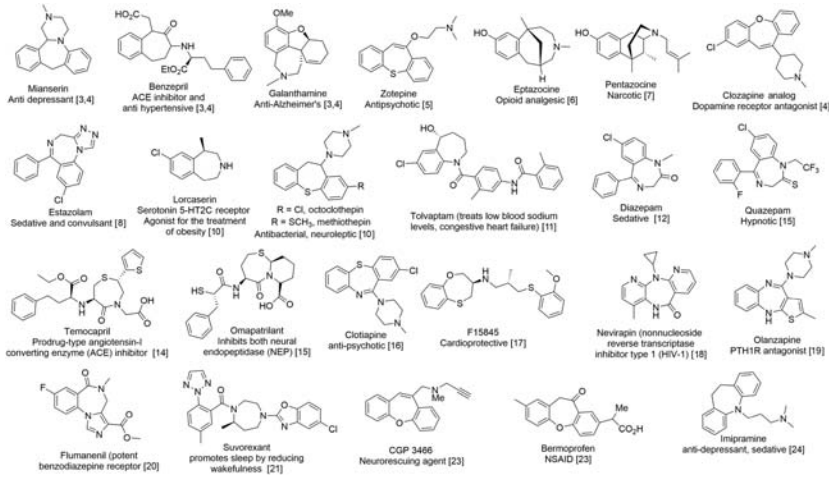


FIGURE 14.1 Pharmaceutically important benz-annulated medium ring−sized heterocyclic compounds.

pharmacological significance. Fig. 14.1 offers few examples of this class of molecules [3−24].

Synthesis of medium ring−sized heterocyclic compounds has, therefore, attracted the attention of synthetic and medicinal chemists [25]. It is known that synthesis of medium-ring structures is plagued by enthalpic and entropic difficulties. Moreover, unfavorable conformational features provide additional problems. This, in turn, has provided scope for the development of newer methodologies to access such ring systems. The majority of the newer developments in this field have embraced the use of several recently developed metal-mediated transformations to overcome some of these difficulties [26]. Applications of green synthetic approaches are, thus, welcome in this domain as well. In the following sections, some of these developments are highlighted and arranged according to the type of the enabling techniques.

In the greener approach to medium ring−sized compounds, various enabling techniques such as microwave (MW), ultrasound, ball milling, and greener reaction mediums such as ionic liquids (ILs), and aqueous media have seen many applications. The advancements made will be briefly reviewed.

14.2 Use of greener solvents

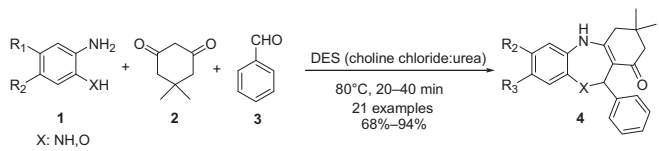
This section deals with the use of a variety of green solvents in the synthesis of title compounds. In the last decade, deep eutectic solvents (DESs) have gained extensive attention. DESs are prepared by mixing high melting components having the ability to form strong hydrogen-bonding interactions in the liquid phase that reduce the ability of the precursors to crystallize [27,28].

DESs are simple to prepare and require inexpensive materials, require little purification, generate little waste, and possess high atom-economical aspects embracing many of the principles of *green chemistry* [29].

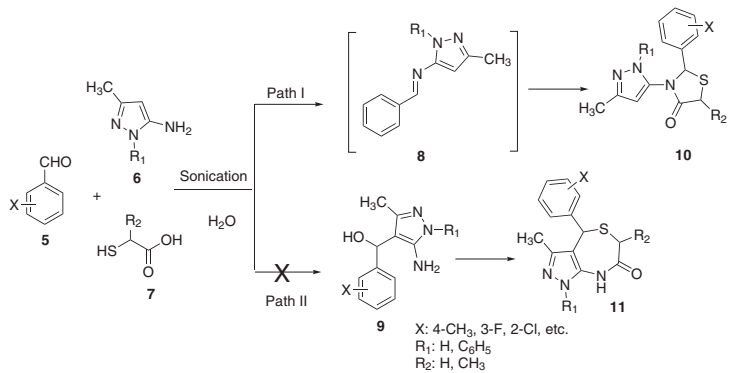
Shaabani et al. reported a combination of choline chloride and urea as a DES for the synthesis of benzo-fused seven-membered heterocycles, including tricyclic 1,4-benzodiazepines and 1,4-benzoxazepines (Scheme 14.1), via a three-component, one-pot reaction [30]. The reaction conditions are relatively mild and do not require acid catalysts, additional metals, or organic solvents. The method has the advantages of short reaction time, excellent yield, an easy workup procedure, and being environment-friendly.

Dandia et al. [31] reported an efficient ultrasound-promoted green method for the synthesis of pyrazolo[3,4-*e*][1,4]thiazepine derivatives **11** in water. The reaction proceeds well without using any catalyst or additive in aqueous medium. A notable feature of the reaction is the formation of a heptacyclic ring system instead of the expected pentacyclic one **10**. The protocol is easy to operate, involves shorter reaction time, and the yield is also very good (Scheme 14.2).

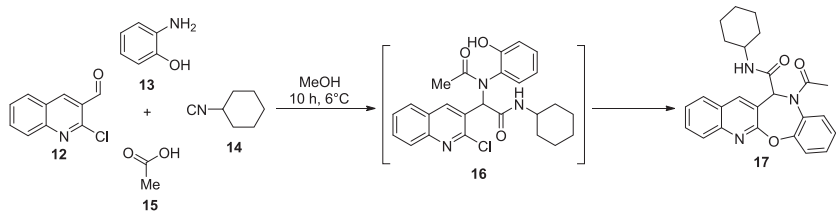
A convenient and facile method was reported by Ghandi et al. for the synthesis of functionalized quino[2,3-*b*][1,5]benzoxazepines **17** (Scheme 14.3) [32]. The compounds were synthesized through a one-pot sequential Ugi-4CR/base-free intramolecular aromatic nucleophilic substitution (S_NAr) reaction in



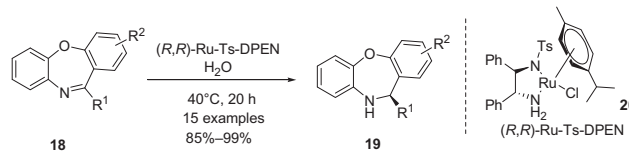
SCHEME 14.1 Synthesis of benzo-fused seven-membered heterocycles via a three-component reaction in DES. *DES*, Deep eutectic solvent.



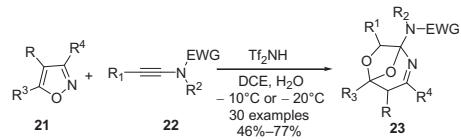
SCHEME 14.2 Synthesis of pyrazole[3,4-*e*][1,4]thiazepine.



SCHEME 14.3 Synthesis of quino[2,3-*b*][1,5]benzoxazepines.



SCHEME 14.4 ATH of benzo[*b*,*f*][1,4]oxazepine in water. *ATH*, Asymmetric transfer hydrogen.



SCHEME 14.5 The reaction of ynamides with 3,5-dimethylisoxazole.

moderate-to-good yields. Thus, when a mixture of 2-chloroquinoline-3-carbaldehyde **12**, 2-aminophenol **13**, acetic acid **15**, and cyclohexyl isocyanide **14** was refluxed in methanol, compound **17** was directly obtained as the sole product in 83% yield within 10 h.

Asymmetric hydrogenation of imines is one of the most prominent methods for directly accessing enantiopure amines. Water-mediated asymmetric transfer hydrogen (ATH) reaction is a green, cost-effective, and operationally simpler approach than molecular hydrogenation. More and Bhanage reported a phosphine-free catalytic ATH protocol for diverse dibenzo[*b*,*f*][1,4]oxazepines **19** (Scheme 14.4) with an unmodified (*R*,*R*)-Ru-TsDPEN complex **20** in aqueous medium [33]. The desired cyclic amine was obtained in high yield ($>95\%$) with excellent enantioselectivity (up to 93% ee) at 40°C in 12 h. Additional advantages of aqueous-mediated ATH methods are nonrequirement of inert atmosphere, use of HCOOH−HCOONa as a green hydrogen source, atom-economy, and the use of water as an environmentally benign solvent.

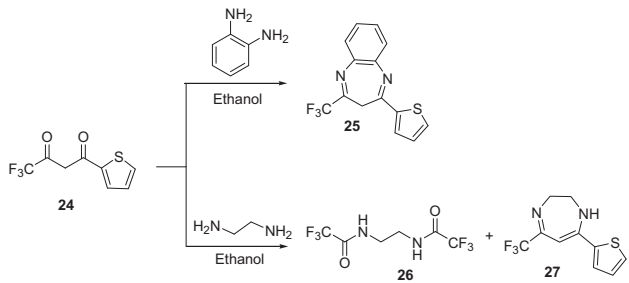
Very recently, a formal [5 + 2 + 1] cycloaddition of ynamides and isoxazoles under Brønsted acid-catalysis in water was reported by Wan and coworkers [34], which provided an atom-economical access to oxygen-bridged tetrahydro-1,4-oxazepines **23** (Scheme 14.5). This methodology not only

enriches the chemistry of ynamides but also provides important insights into the cycloaddition manifold with distinct selectivity.

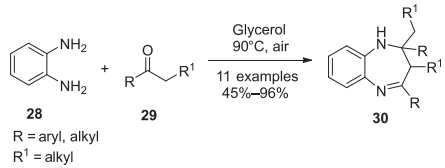
Manzur et al. described a facile synthesis of new diazepine derivatives in ethanol containing the 2-thienyl unit. Thus one-pot double condensation reaction of 2-thienyltrifluoroacetone (2-TTA) **24** (Scheme 14.6) with ethylenediamine or *o*-phenylenediamine, in a 2:1 stoichiometric ratio, leads to the formation of 7-(thiophene-2-yl)-5-(trifluoromethyl)-2,3-dihydro-1*H*-1,4-diazepine 2**5** and 2-thiophene-4-trifluoromethyl-1,5-benzodiazepine **27** in 56% and 53% yields, respectively. The bis(trifluoroacetamide) ethylene derivative **26** was also isolated in 32% yield as a side-product in the reaction of 2-TTA and ethylenediamine.

A simple, efficient, and catalyst-free synthesis of benzodiazepines and benzimidazoles by the condensation of *o*-phenylenediamine with carbonyl compounds in glycerol solvent was reported. The product 1*H*-1,5-benzodiazepines **30** (Scheme 14.7) was obtained in good yield. In addition, glycerol can be reused without purification for further condensation reactions [35].

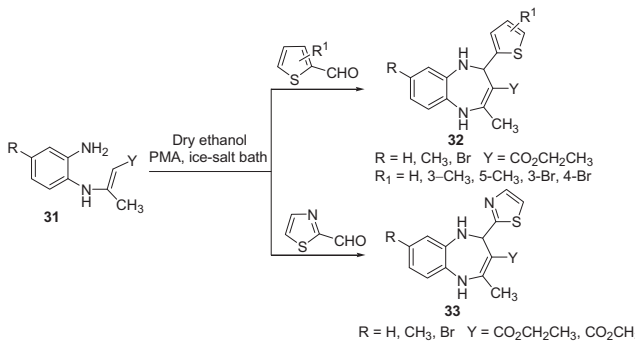
Wang and coworkers [36] reported synthesis of a novel class of benzodiazepines by condensation of enamines of the type **31** (Scheme 14.8) with thiophene aldehyde or thiazole aldehyde in ethanol at 0°C in the presence of a catalytic amount of phosphomolybdic acid. The products **32** and/or **33** were obtained in 80%–90% yield. In vitro antimicrobial activity against *Candida neoformans*, *Candida albicans*, *Escherichia coli*, and *Staphylococcus aureus* were evaluated for all the synthesized 1,5-benzodiazepine derivatives. The most active derivative of the 1,5-benzodiazepine series exhibited biological



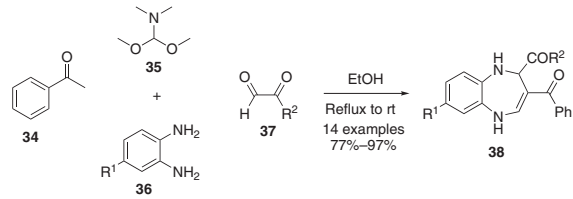
SCHEME 14.6 Synthesis of diazepine.



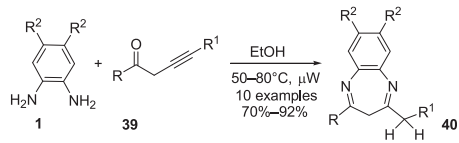
SCHEME 14.7 Synthesis of 1*H*-1,5-benzodiazepines.



SCHEME 14.8 Synthesis of benzodiazepines.



SCHEME 14.9 Synthesis route to 3-acyl-1,5-benzodiazepine.

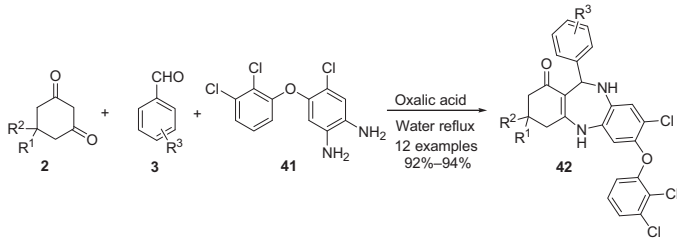


SCHEME 14.10 The synthesis of 1,5-diazepine from alk-3-ynone and *o*-phenylenediamine.

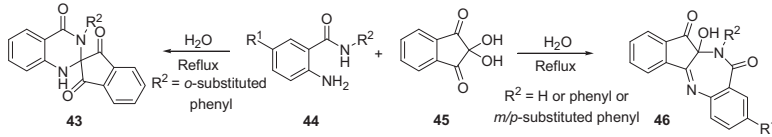
activity and shows considerable potency against all of the tested strains [36]. In particular, compound **33** (when R═H) exhibited excellent antifungal activity and was found to be 32−64 and 9−12.8 times more potent than the reference drugs against *C. neoformans*, respectively.

Very recently, Wang and coworkers developed a novel, catalyst-free one-pot synthesis of diverse 3-acyl-1,5-benzodiazepines **38** (Scheme 14.9) through a domino reaction of *N*,*N*-dimethylformamide dimethyl acetal **35**, aromatic ketones **34**, 1,2-phenylenediamine **36**, and aldehyde derivatives **37** using ethanol as solvent [37]. The main features of this protocol include the use of inexpensive and easily available starting materials, convenient one-pot operation, ease of product purification, good yields, and a broad substrate scope.

Dembinski and coworkers reported a condensation reaction of derivative of *o*-phenylenediamines **1** and alk-3-yn-1-ones **39** subsequently provided a diverse 2,4-disubstituted 1,5-benzodiazepines **40** (Scheme 14.10) with



SCHEME 14.11 Synthesis of dibez[1,4]-diazepine-1-ones catalyzed by oxalic acid in water.



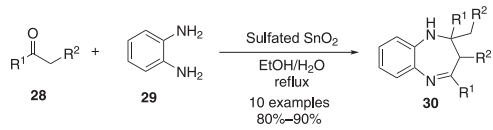
SCHEME 14.12 Reaction of ninhydrin with 2-aminobenzamide derivative.

moderate-to-good yields (70%–92%) using commercial grade ethanol as solvent under MW irradiation [38]. This catalyst-free method includes formation of two C=N bonds and does not require the isolation of the enaminone. The anti-Markovnikov regio-chemistry was observed for the overall formal amination reaction.

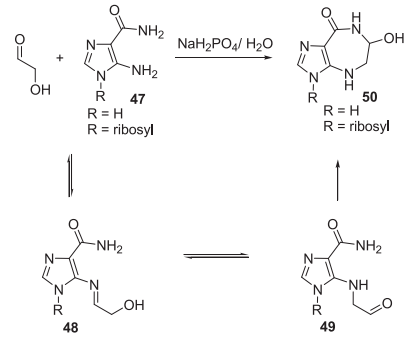
Sangshetti and coworkers also demonstrated a green catalytic process for the synthesis of some new dibenz[1,4]-diazepine-1-one derivatives of the type **42** (Scheme 14.11) [39]; the greener components are the use of oxalic acid as catalyst and water as solvent. The methodology involved a one-pot three-component condensation of aromatic aldehydes, 1,3-diketones, and 1, 2-diamines. Other advantages of this method are good yield (92%–94%), short reaction time, easy workup, simplicity in operation, and mild reaction conditions.

An efficient synthesis of 11a-hydroxy-11,11a-dihydrobenzo[*e*]indeno[2, 1-*b*][1,4]diazepine-10,12-dione derivatives **46** (Scheme 14.12) through an unprecedented condensation of ninhydrine **45** [40] with amino-*N*-phenylbenzamide **44** in aqueous environment was reported. The reaction proceeds through double-nucleophilic attack on C-2 of ninhydrin when a 2-amino-*N*-phenylbenzamide derivative **44** bears an *ortho*-substituent in the *N*-phenyl group. Since the 1,4-benzodiazepine scaffold is encountered in several biologically and pharmacologically active products, this protocol may serve as a platform for the synthesis of a diverse array of potentially active molecules from simple starting materials.

Munde and coworkers reported a mild protocol for the synthesis of 1, 5-benzodiazepines derivative **30** (Scheme 14.13) at ethanol/water (1:1) reflux condition [41]. The methodology involved condensation of phenylenediamine



SCHEME 14.13 Synthesis of 1,5-benzodiazepines.



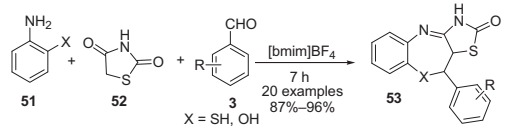
SCHEME 14.14 The synthesis of azepinomycin (R = H) azepinomycin riboside (R = ribofuranosyl) in water.

28 with various ketones **29** using sulfated tin oxide (25 mol%) as a heterogeneous catalyst. The offered method revealed 80%−90% yield of 1,5-benzodiazepines **30**. The sulfated tin oxide catalyst was salvaged by a simple filtration.

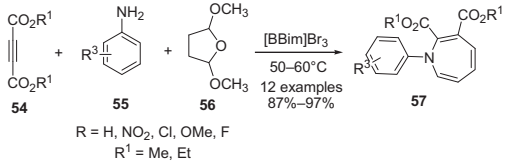
Powner et al. described an atom-economic, high-yielding, chromatography-free, and protecting-group-free strategy for the synthesis of azepinomycins **50** (Scheme 14.14) by condensation of glycolaldehyde with 5-amino-imidazole-4-carboxamide **47** using water as solvent and sodium dihydrogenphosphate as catalyst [42]. The protocol demonstrated the pH dependence of an amino-imidazole tethering strategy that uses an Amadori rearrangement.

14.3 Use of ionic liquids in organic synthesis

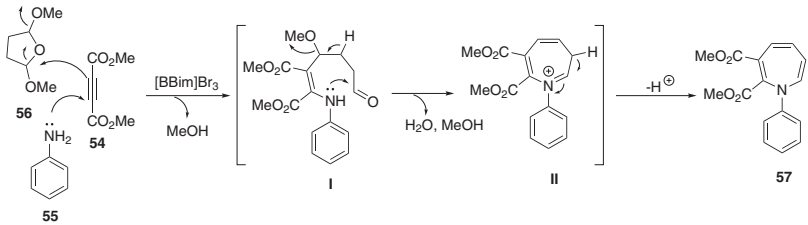
The use of ILs as alternative reaction media to traditional molecular solvents is a rapidly growing field. ILs have many advantages such as negligible vapor pressure, tunable miscibility, ease of product isolation, thermal robustness, recyclability, and reusability. They have also been referred to as *designer solvents* as their chemical and physical properties could be adjusted by a careful choice of cation/anion. Room temperature ILs based on 1-alkyl-3-imidazolium cation has shown great promise in a variety of organic transformations. Moreover, outcomes of many of these reactions such as regioselectivity and chemo-selectivity may differ on changing to an IL as solvent. In addition, occasional catalytic activity has also been recorded which has been attributed to the inherent Brønsted and Lewis acidities of the ring hydrogens H-2, H-4,



SCHEME 14.15 Synthesis of thiazepines and oxazepines in ionic liquid.



SCHEME 14.16 Synthesis of *N*-substituted azepine derivatives.



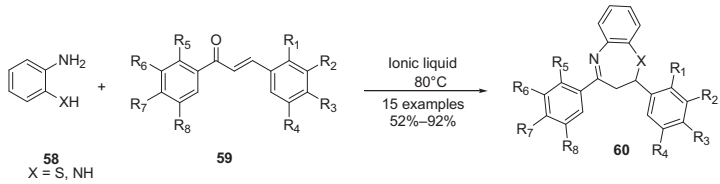
SCHEME 14.17 A plausible mechanism for the formation of *N*-substituted azepine derivatives.

and H-5 of the imidazolium cation in [bbim]Br. All these factors have prompted the use of ILs in the synthesis of heterocycles. Some of the applications in the medium ring−sized heterocycles are briefly reviewed herein.

Kommidi and coworkers reported an eco-friendly method for the synthesis of thiazepines and oxazepines **53** (Scheme 14.15) of thiazolidine 2,4-dione **52** in high yields through a one-pot, three-component reaction between cyclic ketone, substituted aromatic aldehyde, and 2-amino phenol or 2-amino thiophenol using [bmim]BF4 as the IL at room temperature [43]. The IL, [bmib]BF_4, not only improved the yields but also drastically reduced the reaction time.

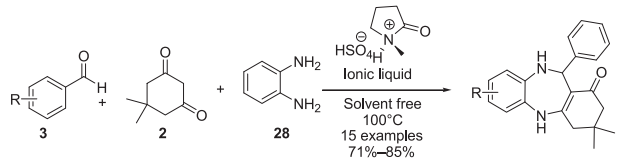
An environmentally benign, IL endorsed multicomponent method to N-substituted azepines has been reported involving coupling of aromatic amines **55**, dimethyl acetylene dicarboxylate **54**, and 2,5-dimethoxytetrahydrofuran **56** in the presence 1,3-di-*n*-butylimidazolium tribromide [BBim]Br_3 as reaction medium and catalyst (Scheme 14.16) [44]. The products **57** were obtained in very good yields. The key benefit is the recyclability of the IL used. A possible mechanism for the transformation is shown in Scheme 14.17.

Very recently, Sakirolla and coworkers have developed an elegant, new, and environment-friendly method for the synthesis of 1,5-benzothiazepines



R1	R2	R3	R4	R5	R6	R7	R8	Yield (%)
H	H	H	H	H	H	H	H	52
H	H	H	H	OH	H	H	H	92
H	H	OMe	H	OH	H	H	H	91

SCHEME 14.18 Synthesis of 1,5-benzodiazepines and 1,5-benzothiazepines.



R = H, *p*-NO_2, *o*-NO_2, *m*-NO_2, *p*-Cl, *o*-Cl, *o*-OH etc

SCHEME 14.19 Synthesis of 4-substituted-1,5-benzodiazepines.

and 1,5-benzodiazepine using di-cationic liquid as a solvent cum catalyst by the reaction of *o*-aminothiophenol **58** with a variety of chalcones **59** (Scheme 14.18) under mild reaction conditions [45]. The reaction was proposed to proceed through a 1,4-conjugate Michael addition of chalcone with *o*-phenylenediamine or *o*-aminothiophenol followed by a cyclo-condensation reaction to give desired 1,5-benzodiazepines and 1,5-benzothiazepines **60**.

Naeimi and Foroughi reported an efficient, nontoxic, inexpensive and environmentally benign method for the one-pot synthesis of 4-substituted-1,5-benzodiazepines **4** via the three-component reaction of a series of aldehydes **3** with dimedone **2** and *o*-phenylenediamine **28** using [H-NMP][HSO_4] as a Brønsted acidic IL catalyst under solvent-free conditions (Scheme 14.19) [46]. Initially, Michael addition reaction of dimedone with activated *o*-phenylenediamine provides an enamine intermediate (not isolated), which then reacts with the aromatic aldehyde to give the corresponding imine that in turn undergoes an intramolecular cyclodehydration reaction to furnish 4-substituted-1,5-benzodiazepines.

14.4 Microwave-assisted synthesis

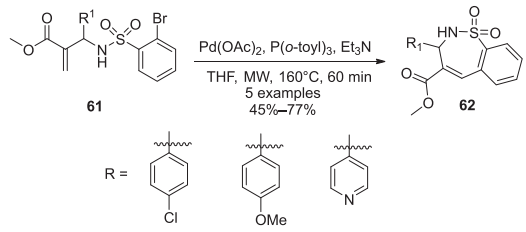
MW-assisted synthesis is a good technique in the field of green chemistry and manages a flexible platform for heterocycle ring formation. MW-assisted

reactions have quickly become a robust and efficient tool in synthetic organic chemistry. In recent years a large number of reports appeared through MW-assisted synthesis of *S*-containing heterocycles. The importance of *S*-containing heterocyclic compounds for biomedical [47] and material science applications [48] has led to an increase in the number of synthetic methods available for the preparation of this type of heterocyclic compounds [49,50].

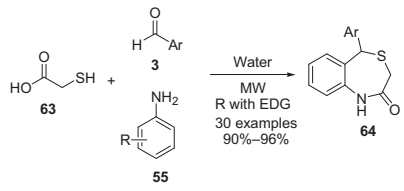
Vasudevan and coworkers described bromo-substituted *aza*-Baylis–Hillman adducts **61** (Scheme 14.20) as a useful scaffold for the synthesis of benzo-fused thiazepine-1,1-dioxides **62** via facile intramolecular Heck cyclization under MW irradiation in the presence of $Pd(OAc)_2$, P(*o*-tolyl)$_3$, and triethylamine in tetrahydrofuran (THF) at a ceiling temperature of 160°C for 60 min [51].

The supreme advantage of MW-assisted synthesis resides in the extraordinary acceleration of reaction rate conducted in unconventional reaction media. The use of water as a nonflammable and economical alternative to conventional organic solvents has attracted a great deal of attention as the high dielectric constant of the former allows efficient absorption of MW irradiation [52]. Tu and coworkers described a highly efficient synthesis of benzothiazepinones in a chemoselective fashion via an MW-assisted three-component reaction of an aromatic aldehyde with aniline and mercaptoacetic acid **63** (Scheme 14.21) [53]. The reaction furnished the best results in water at 110°C, and benzothiazepinones **64** were synthesized in 90%–96% yield under the optimum reaction conditions.

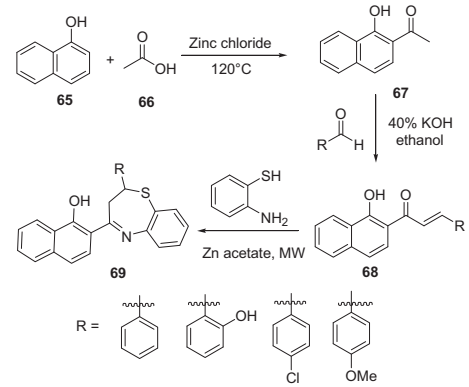
Nikalje and coworkers described a synthesis of 1,5-benzothiazepines **69** (Scheme 14.22) in a solvent-free condition involving cyclo-condensation of 1,3-substituted prop-2-en-1-one **68** with 2-aminothiophenol in the presence



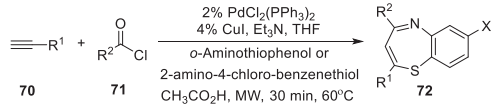
SCHEME 14.20 Microwave-assisted synthesis of benzothiazepine-1,1-dioxide.



SCHEME 14.21 Microwave-assisted synthesis of benzothiazepinones.



SCHEME 14.22 Synthesis of 1,5-benzothiazepines.

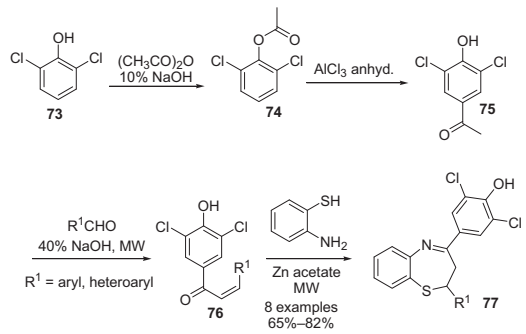


SCHEME 14.23 Synthesis of 2,4-disubstituted benzo[*b*][1,5]thiazepines.

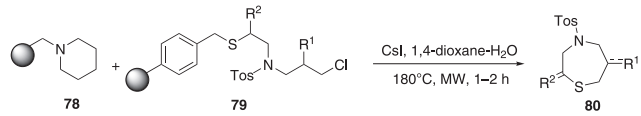
of eco-friendly catalyst zinc acetate under MW irradiation [54]. The starting prop-2-en-1-one **68** was prepared by the acetylation of α-naphthol with acetic acid and subsequent treatment of acetylated α-naphthol with an aromatic aldehyde.

A series of 2,4-disubstituted benzo[*b*][1,5]thiazepines **72** (Scheme 14.23) were synthesized by a condensation of an in situ prepared ynone with 2-amino-4-chlorothiophenol under MW irradiation using acetic acid as solvent. Substituted acid chloride **71** and acetylene derivative **70** were first reacted under Sonogashira conditions at room temperature to deliver the expected alkynone; subsequent addition of *o*-aminothiophenol or 2-amino-4-chloro benzenethiol in a Michael fashion [55,56]. This optimization of cyclization clearly showed that dielectric heating is superior to conductive heating.

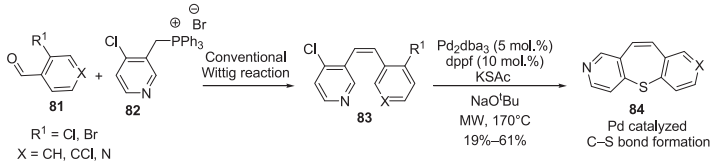
Nikalje and Vyawahare reported an efficient, one-pot, solvent-free, MW-assisted green synthesis of a range of 1,5-benzothiazepine derivatives **77** (Scheme 14.24) [57] using a cyclo-condensation of 1,3-substituted prop-2-en-1-one **76** with 2-aminothiophenol in the presence of zinc acetate as eco-friendly catalyst. The 1,5-benzothiazepine derivatives were synthesized from 2,6-dichloroacetophenone **75** which, in turn, was obtained by *para*-selective Fries rearrangement of 2,6-dichloro phenyl acetate **74**. The preparation of chalcones in a conventional protocol required Claisen–Schmidt condensation for 48 h for completion of reaction, whereas MW-assisted synthesis required only 5–10 min and gave better yields.



SCHEME 14.24 Synthesis of 2,4-substituted-1,5-benzothiazepines.



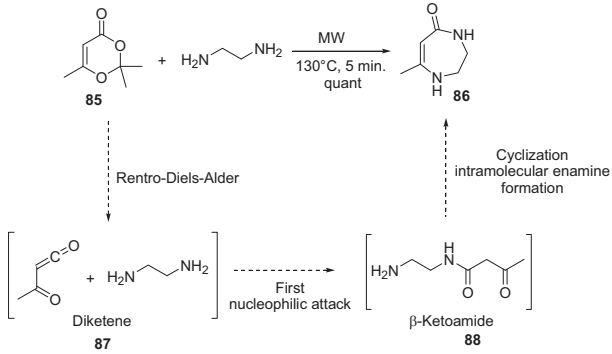
SCHEME 14.25 Synthesis of thiazepines.



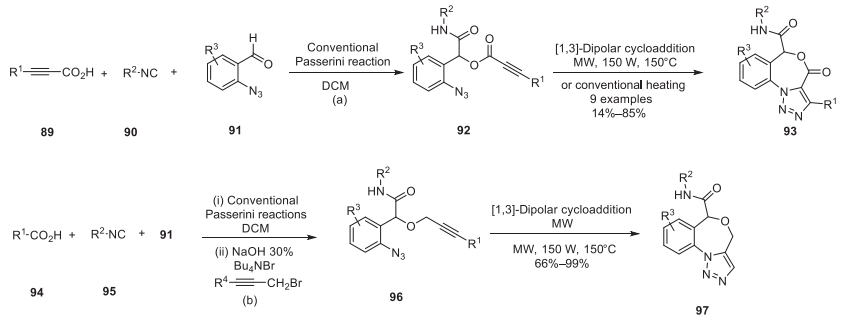
SCHEME 14.26 Synthesis of dibenzo[*b*,*f*]thiepines through Pd-catalyzed double C–S formation.

A clever approach for the synthesis of 1,4-thiazine derivatives which involved ring closure of **79** (Scheme 14.25) followed by iodide-mediated traceless cleavage of the resin in the presence of a polymer-supported base **78** as an HCl scavenger was reported [58,59]. The MW-assisted cyclization was undertaken in a dioxane–water mixture using CsI at 180°C. The desired seven-, eight-, and nine-membered sulfides were isolated in excellent yields. The ring closure under MW-irradiated conditions yielded an excellent 88% yield in comparison with a meager 24% yield under conventional heating.

Božinović and coworkers disclosed a strategy for the synthesis of dibenzo[*b*,*f*]thiepines **84** (Scheme 14.26) using potassium thioacetate as a source for sulfur in a double palladium-catalyzed C–S bond formation [60]. MW-activation for this double C–S bond formation reduces the reaction times (from 14 h to 90 min) and enhances the yield as well (from 30% to 50%). However, crucial to the success of the reaction was the choice of a suitable phosphine ligand, and 1,11-bis(diphenylphosphino)ferrocene was found to be better for this double C–S bond formation.



SCHEME 14.27 Solvent-free synthesis of 1,4-diazepines through retro-Diels–Alder and intermolecular enamine formation.



SCHEME 14.28 Synthetic route to triazolo-fused benzoxazepinones and benzoxazepines via successive Passerini and [1,3]-dipolar cycloaddition.

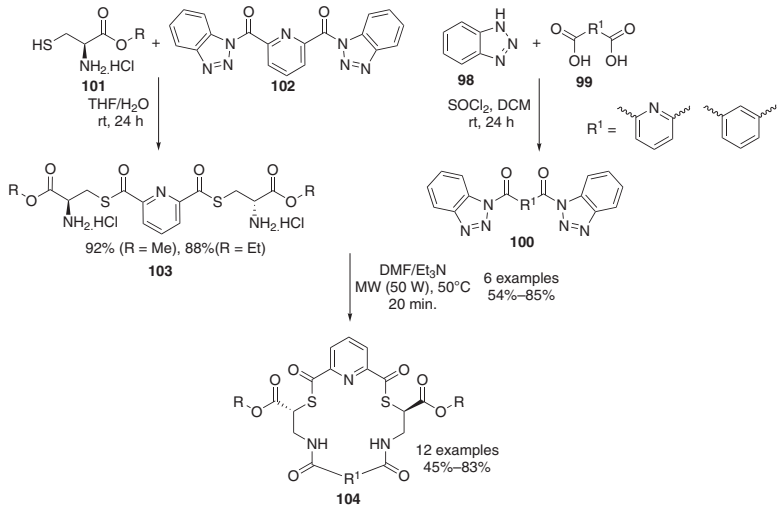
Petros and coworkers described a solvent-free synthesis of 1,4-diazepines of the type **86** (Scheme 14.27). In this preparation, 2,2,6-trimethyl-4*H*-1, 3-dioxin-4-one **85** and linear bis-amines were condensed at 130°C under MW-irradiation condition [61]. The diazepines formed as the sole product within only 5 min. Mechanistically, it begins with a retro-Diels–Alder reaction leading to the diketene, which undergoes a nucleophilic attack by a linear bis-amine to generate the intermediate β-keto amide **87** which then undergoes an intermolecular cyclization through enamine formation.

Basso and coworkers reported an elegant synthesis of unprecedented triazole fused benzoxapinone **93** and benzoxazepines **97** involving a conventional 3-component Passerini reaction with an MW-assisted azide-alkyne [1,3]-dipolar cycloaddition [62]. The [1,3]-dipolar cycloaddition leading to the benzoxazepinones **93** (Scheme 14.28) could be performed either under conventional heating or under MW irradiation. Under the conventional heating the reaction proceeded rather sluggishly but generally led to cleaner products. In marked contrast, the cycloaddition leading to the benzoxepine **93** is easily achieved under MW irradiation.

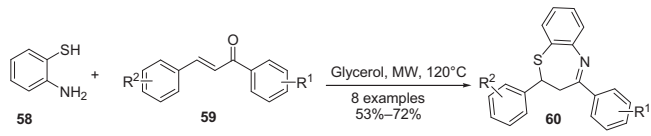
An interesting example of peptidomimetic cyclization has been recently reported by Ibrahim et al. through an MW-assisted thioether bond formation between an *N*-acylbisbenzotriazole **100** (Scheme 14.29) and a dicysteine ester hydrochloride **103** [63]. The *N*-acylbisbenzotriazole was obtained by mixing appropriate dicarboxylic acids **99** and 1*H*-benzotriazole **98** in the presence of thionyl chloride. The second scaffold **104** was synthesized by regioselective *S*-acylation of cysteine esters. The resulting pyridine dicysteine ester hydrochlorides were subsequently treated with *N*-acylbisbenzotriazoles in the presence of triethylamine under MW irradiation for 20 min to afford the cyclic and enantiopure peptidomimetics via double *N*-acylation in moderate-to-good yields.

Very recently, Jagrut and coworkers reported an efficient and eco-friendly synthesis of 1,5-benzothiazepines **60** by the reaction of various derivatives of 2-propen-1-ones **59** with 2-aminothiophenol **58** using MW irradiation in greener reaction medium, glycerol with a ceiling temperature 120°C [64] (Scheme 14.30).

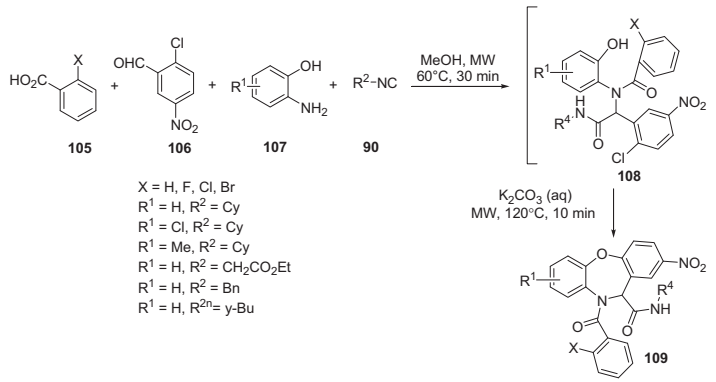
A series of dibenz[*b*,*f*][1,4]oxazepine of the type **109** (Scheme 14.31) were synthesized in an efficient manner by a Ugi four-component reaction and MW-assisted intramolecular Ullmann etherification [65] involving 2-aminophenols and 2-bromobenzoic acids or 2-bromobenzaldehydes. The



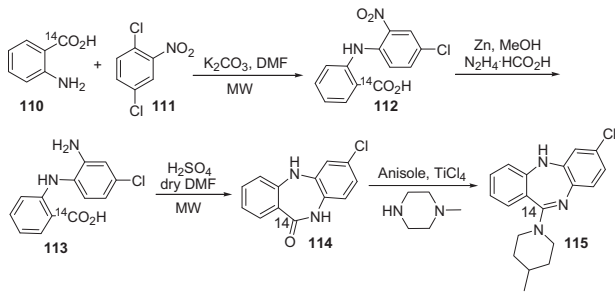
SCHEME 14.29 Example of peptidomimetic cyclization through an MW-assisted thioester bond formation.



SCHEME 14.30 Synthesis route for 1,5-benzothiazepine from chalcones and *o*-aminothiol.



SCHEME 14.31 One-pot synthesis of dibenz[*b*,*f*][1,4] oxazepines via U-4CR-S_NAr.



SCHEME 14.32 Microwave-assisted synthesis of clozapine.

synthesis was carried out at 50°C−60°C in MeOH for 2−3 days to form a series of 22 linear products in 46%−90% yields. An intramolecular Ullmann etherification was then carried out on **108** (not isolated) in the presence of MW irradiation to obtain the cleft shaped 6/7/6-fused tricyclic heterocycles. The intramolecular Ullmann diaryl ether formation was catalyzed by 10 mol% of CuI and 30 mol% of *N*,*N*-dimethylglycine hydrochloride in the presence of Cs_2CO_3 with MW irradiation heating at 150°C for 30 min to furnish dibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-ones and dibenz[*b*,*f*][1,4]oxazepin-11(10*H*)-carboxamides in 64%−100% yields.

Clozapine **115** (Scheme 14.32), the most effective antipsychotic drug for treatment-resistant schizophrenia [66], was prepared by an MW-assisted four-step synthesis from anthranilic acid (C14-carboxylic) with good overall radiochemical yield. The key intermediate, [carboxyl-^{14}C]-2-[(4-chloro-2-nitrophenyl)amino]benzoic acid **112**, was furnished by the Ullmann condensation reaction between [carboxyl-14C] anthranilic acid **110** and 1,4-dichloro-2-nitrobenzene **111** under MW irradiation [67]. Subsequent reduction of the nitro group with hydrazinium monoformate at room temperature led to the

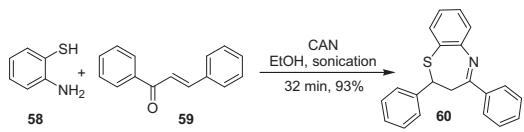
[carboxyl-^{14}C]-2-[(4-chloro-2-aminophenyl)amino]benzoic acid **113**. Cyclization of amino benzoic acid was carried out in DMF in the presence of catalytic amounts of H_2SO_4 under MW irradiation. Finally, condensation of the cyclic amide **114** with 1-methylpiperazine in the presence of $TiCl_4$ provided the desired [11−^{14}C]-8-chloro-11-(4-methyl-1-piperazinyl)-5*H*-dibenzo[*b*,*e*][1,4] diazepine **115**.

14.5 Ultrasound as an enabling technique

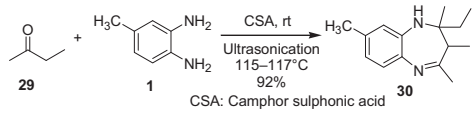
Ultrasound irradiation has been extensively used in organic synthesis in the last three decades [68−71]. It is a relatively new approach for the interaction of matter and energy which promotes chemical and physical changes. The conventional reactions that use strongly acidic conditions, reagents, high temperatures, lingering reaction times, inconsistency with other functional groups, and unsatisfactory yields have been improved by ultrasound irradiation [72−75]. Mechanistically, the molecules of the liquid will form cavitation bubbles under a strong ultrasonic irradiation. It is the collapse of the bubbles in succeeding compression cycles which generates the energy for chemical and mechanical effects. Under ultrasonic irradiation, organic transformations occur in high yield, short reaction times, or milder conditions [76−82]. Ultrasonic-assisted technique is increasingly used for the acceleration of organic reactions and it is an environment-friendly synthetic protocol [83−89].

An efficient, eco-friendly, ultrasound-mediated synthesis of 1,5-benzothiazepine **60** (Scheme 14.33) involving a condensation between chalcones and *o*-aminothiophenol using 10 mol% ceric ammonium nitrate as catalyst in ethanol was reported. The generality of the reaction was tested with many substituted heterocyclic and homocyclic chalcones with *o*-aminothiophenol and the yields were generally very good. The protocol was compatible with many substituents such as NO_2, F, CH_3, Cl, and OCH_3, and for the substrates having CH_3, aryl, or OCH_3 groups, no competitive nucleophilic cleavage was observed. In the case of hetero-aryl aldehydes, no significant substituent influence was noted [90,91].

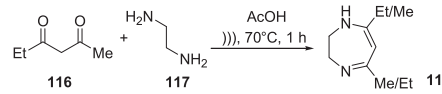
Shingare and coworkers described a synthesis of 1,5-benzodiazepine derivatives **30** (Scheme 14.34) under ultrasonication using camphorsulfonic acid as catalyst but without using any solvent. The mechanism of camphorsulphonic acid-catalyzed cyclo-condensation for the synthesis of 1,5-benzodiazepines was also proposed [92].



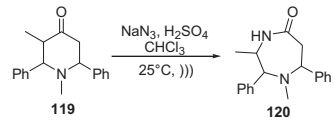
SCHEME 14.33 Synthesis of 1,5-benzothiazepine.



SCHEME 14.34 Synthesis of 1,5-benzodiazepine.



SCHEME 14.35 Synthesis of 2,3-dihydro-1*H*-1,4-diazepine.



SCHEME 14.36 Synthesis of diazepine.

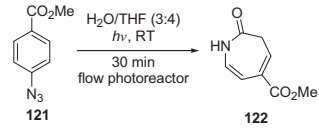
Diazepine derivative **118** (Scheme 14.35) was synthesized by the reaction of 1,2-diaminoethane **117** and hexane-2,4-dione **116** under reflux (thermal) in glacial acetic acid for 1 h with high yield. Use of ultrasound (at 60°C−70°C) significantly enhanced the reaction rate [93−99].

Reddy and coworkers reported an interesting heterocycle synthesis using ultrasound irradiation. The diazepine**120** (Scheme 14.36) was synthesized from 1,3-dimethyl-2,6-diphenyl-4-piperidone **119** by using sodium azide in chloroform under ultrasound irradiation. A Schmidt reaction [100] followed by Beckmann rearrangement [101] was utilized for ring expansion reaction of 1,3-dimethyl-2,6-diphenyl-4-piperidone **120** [102].

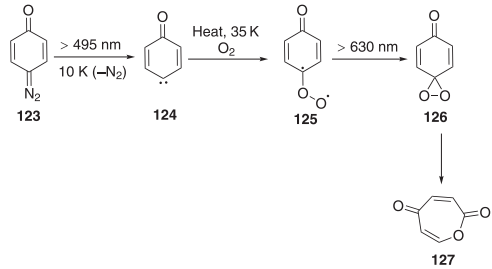
14.6 Photochemical transformations

The discovery of organic photochemistry in the late 19th century has later emerged as a remarkable field in modern organic synthesis [103−106]. The chemical nature of a molecule has been modified by photochemical excitation as an electronic configuration of the molecule is changing. The redox potentials alter in such a way that electron transfer becomes possible. It has been applied to the generation of reactive intermediates of radical reactions [107,108]. Compared to ground-state reactions, these photochemical transformations do not need any chemical activation of the substrates for C−C bond formation, which could lead to side products. These reactions should, therefore, be considered in the context of sustainable process [109,110].

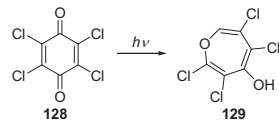
Smalley and coworkers described a synthesis of 3*H*-azepinone ring system by photolysis of aryl azides in water [111,112]. The photolysis



SCHEME 14.37 Synthesis of 3*H*-azepinone.



SCHEME 14.38 Synthesis of oxepine-2,5-dione.



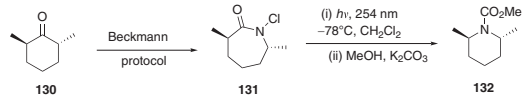
SCHEME 14.39 Synthesis of oxepine.

of methyl 4-azidobenzoate **121** (Scheme 14.37) in water and THF afforded 45% yield of 122 in 20 h. Later, the yield was improved when a 4:3 mixture of THF–water was used. The best balance between productivity and conversion was noted at 0.030 M optimum concentration.

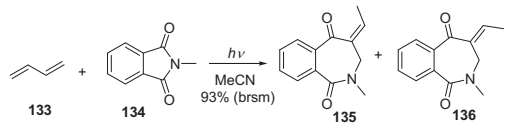
Nuss accomplished a synthesis of oxepine-2,5-dione **127** (Scheme 14.38), a seven-membered oxygen heterocycle, from six-membered carbocycles. The intermediate was formed by the reaction of triplet oxygen and cyclohexadienone carbine **125** [113]. The furnished dioxirane **126** was isomerized to seven-membered oxepine-2,5-dione **127**.

In the similar line, Nuss described a synthesis of oxepin derivative **129** (Scheme 14.39) in 70%–95% yield on the photochemical rearrangement of chloroanil **128** [113].

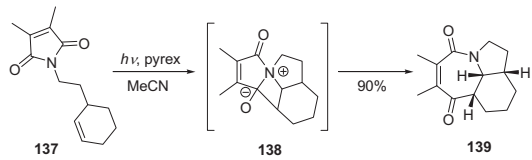
Spino et al. described synthesis of azepane derivative **131** from the ketone **130** following Beckmann protocol (Scheme 14.40). A novel photochemical ring-contraction of the seven-membered *N*-chloro lactum **131** to the six membered lactum **132** [114].



SCHEME 14.40 Synthesis and photochemical rearrangement of azepine amides.



SCHEME 14.41 Synthesis of benzazepines.

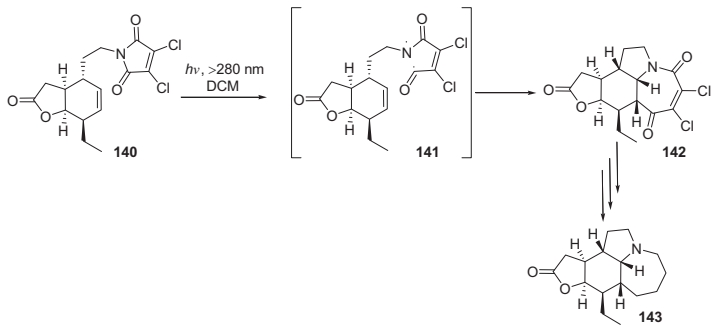


SCHEME 14.42 Synthesis of 5,6-dimethyl-hexahydroazepinoindol.

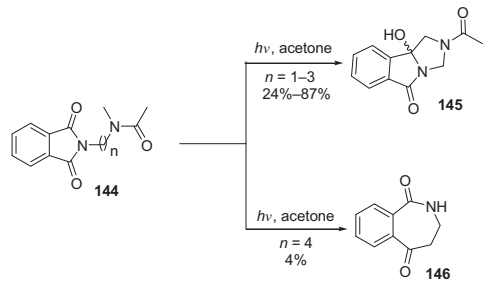
A photochemical irradiation of *N*-methylphthalimide **134** (Scheme 14.41) with butadiene **133** in acetonitrile furnished benzazepinediones **135** and **136** [115,116] with high yield (93%) as an isomeric mixture through [π2 + σ2] photocycloaddition. In the presence of 1,3-pentadiene and isoprene, reaction also occurred and the products were obtained in 50% and 49% yields, respectively. When the authors used 2,5-dimethyl-2,4-hexadiene and cyclopentadiene, or when *N*-phenylphthalimide or phthalimide instead of *N*-methylphthalimide, no reaction was observed.

Booker-Milburn et al. manifested an extremely inspiring use of the Paternò−Büchi reaction for the synthesis of azepinoindole. Thus the tricycle hexahydroazepinoindole **139** (Scheme 14.42) was obtained in high yield by the rearrangement of the intermediate **138**. The hexahydroazepinoindole **139** is an essential scaffold in many alkaloids, such as tuberostemonine, neotuberostemonine, and stenine. These alkaloids have long been used in China and Japan as human cough remedies and antihelminthics in domestic animals [117,118].

Booker-Milburn et al. later synthesized the stemona alkaloid (−)-neostenine **143** (Scheme 14.43) by utilizing the unusual intramolecular [5 + 2] photocycloaddition of maleimides [119]. The starting compound was irradiated in a continuous flow reactor for 1 h at room temperature which furnished the tetracyclic product with 63% yield [120]. The authors explained the product formation by invoking 1,5-singlet diradical **141** formation as an intermediate, which underwent the cycloaddition [121].



SCHEME 14.43 Synthesis of (−)-neostenine.

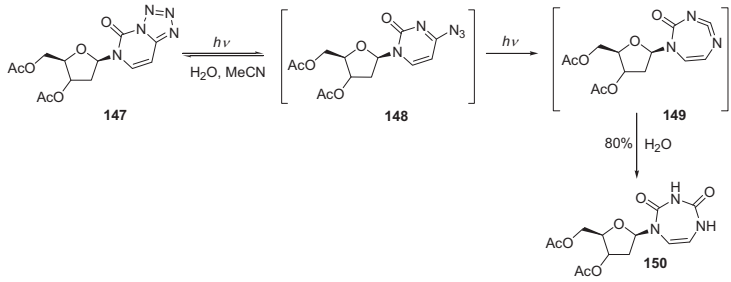


SCHEME 14.44 Synthesis of benzazepinedione.

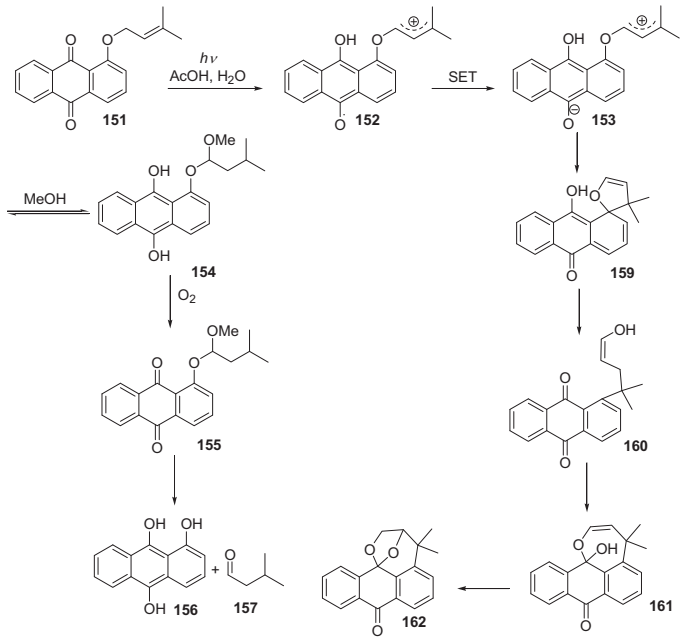
A cyclization reaction of *N*-acyl containing phthalimide **144** (Scheme 14.44) was also observed in an intramolecular fashion [122]. When propylene, ethylene, and methylene bridges were used in place of the *N*-methyl group, irradiation in acetone furnished tricyclic amide **145**. A prolonged irradiation provided only poor amount of unsubstituted benzazepinedione **146** instead. A γ-hydrogen abstraction followed by ring expansion and then Norrish-II cleavage was invoked for the formation of **146**. The photocyclization of succinimide derivatives also furnished similar results [123].

The triazepindione nucleoside analog **150** was prepared by employing an extrusion of nitrogen from tetrazolo[1,5-*a*]pyridines (2-azidopyridines) **147** (Scheme 14.45) [124–126]. The open azido **148** form and tetrazolo[1,5-*a*] pyrimidin-5(6*H*)-one (4-azidouracil) **149** derivative is in photochemical equilibrium. The elimination of N_2 from azido form provided a nitrene species which immediately underwent ring expansion. The final product was obtained by the addition of water to the carbodiimide moiety [121].

Jones and coworkers described synthesis of benzoxepine **162** derivative by a photochemical irradiation of substituted anthraquinone **151**. The authors have found that the loss of water under anaerobic conditions from dihydroquinone intermediate formed a zwitterionic structure **153** (Scheme 14.46) [127].



SCHEME 14.45 Synthesis of triazepinone.

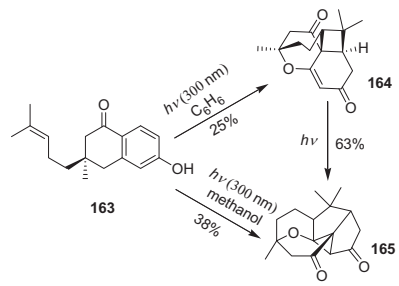


SCHEME 14.46 Synthesis of 4,4-dimethyl-3,4-dihydro-2*H*-anthra[9,1-*bc*]oxepin-8(12bH)-one.

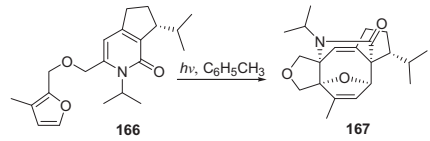
This zwitterionic intermediate then forms a spiro compound **159** through a capture of an allylic carbocation via an aromatic electrophilic substitution. The enol was formed by rearomatization and lactolization. Finally, cyclization provided benzoxepine [128].

It is well known that *ortho*-photocyclo-adducts are very much unstable. Kalena and coworkers reported an excellent example in which 2-alkenyl-7-hydroxy-4-chromanone **163** (Scheme 14.47) formed a tetracyclic compound via *ortho*-photocycloaddition [129].

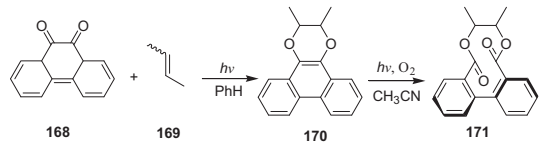
McNSieburth and coworkers reported an interesting intramolecular [4 + 4] photocycloaddition of 2-pyridone with a furan ring which furnished a



SCHEME 14.47 Synthesis of tetracyclic compounds.



SCHEME 14.48 Synthesis of 1,5-cyclooctadiene.

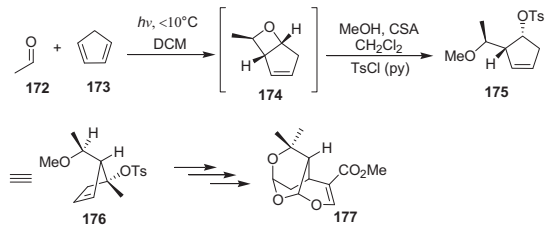


SCHEME 14.49 Synthesis of dioxinophenanthroline or dioxinophenanthrene.

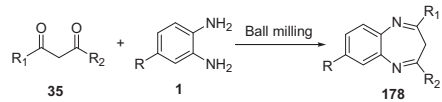
bridged oxepine **167** (Scheme 14.48) [130]. The necessity of the isopropyl group on the nitrogen of pyridone was demonstrated. The *N*-unsubstituted pyridine afforded the desired *cis*, *syn*-product in 25% yield and the *trans, syn*-isomer in major amounts.

A [4 + 2]-photocycloaddition of cyclic diketone like 9,10-phenanthrenequinone **168** with olefins produced relatively stable 1,4-dioxins **171** (Scheme 14.49). The authors also investigated the photochemical conversion of 1,4-dioxins. A biaryl possessing medium-ring bis-lactone was formed through a photocycloaddition–photooxidation reaction sequence through the formation of 1,4-dioxin intermediate **170** [131] with yields up to 90% [132].

A Paternò–Büchi product was isolated by the reaction of the cyclopentadiene **173** (Scheme 14.50) and acetaldehyde. Hoye and Richardson described a ring opening of the Paternò–Büchi product **175** at C_5 by methanolysis which resulted in inversion of configuration at this center, for the synthesis of (−)-sarracenin **177** [133]. The tosylated secondary alcohol underwent a nucleophilic substitution with an appropriate enolate along the synthesis of the natural product (−)-sarracenin **177**.



SCHEME 14.50 Synthesis of (−)-sarracenin.



SCHEME 14.51 Synthesis of benzodiazepine derivative.

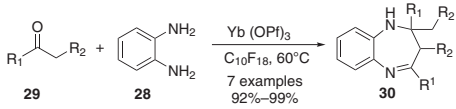
14.7 Use of ball milling

Ball milling is a mechanical technique that is broadly used to grind powders into fine particles [134–141]. The reactants are generally broken apart using solvent molecules in the traditional method; but in ball milling, reactants are broken by using mechanical forces. The term mechanochemistry has been introduced very recently [142]. The use of ball milling in the synthesis and reactions of organic compounds have been published in many review articles [142–146]. The application of solvent-free ball milling in organic synthesis is relatively rare. However, in the last decade, this technique has attracted growing interest because of its simplicity, low cost, and environment friendliness, as well as its capability to achieve very high yields. On the basis of these aspects, research will definitely increase in future in basic and applied science fields (Scheme 14.51).

Carlier and coworkers described that reaction between diamines **1** and 1,2- or 1,3-dicarbonyls by ball milling provided benzodiazepine **178** derivatives without any catalyst or solvent [147]. These products were also obtained in high yields.

14.8 Use of fluorous techniques

Horváth and Rábai commenced a new approach to the heterogenization of homogeneous catalysts called fluorous biphase catalysis in 1994 [148]. The approach is very similar to that in the aqueous biphase system, the replacement of aqueous phase with perfluorocarbon solvents that are immiscible with the most common organic solvents at ambient temperature. Fluorous ponytail is simply a long perfluoroalkyl groups used as a catalyst that can be anchored in the fluorous solvent while the substrates and products are



SCHEME 14.52 Synthesis of 1,5-benzodiazepine derivative.

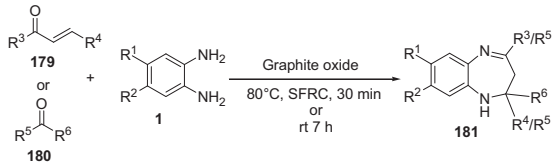
preferentially soluble in the upper organic phase. The fluorous biphase system becomes monophasic upon heating or under pressure which allows genuine homogeneous catalysis to occur. In recent years, this technique employs a perfluoroalkyl chain (Rf) as a "phase tag" which also provides a homogeneous reaction environment compatible with the employment of other enabling techniques such as MW and ultrasound [149].

Cai and coworkers described a synthesis of 1,5-benzodiazepines **30** (Scheme 14.52) by using $Yb(OPf)_3$ as fluorous catalyst. The authors observed that the condensation also proceeded smoothly to give the desired product when using perfluorotoluene (C_7F_8) and perfluoromethylcyclohexane (C_7F_{14}) as fluorous solvents. However, it is impossible to recover the fluorous phase by phase separation as perfluorotoluene is in fact miscible with reaction substrates such as acetone at room temperature. In addition, the loss of fluorous solvent is very serious issue when using perfluoromethylcyclohexane (C_7F_{14}) as a fluorous solvent because it is very volatile (bp 76°C) during repeated condensation reactions [150].

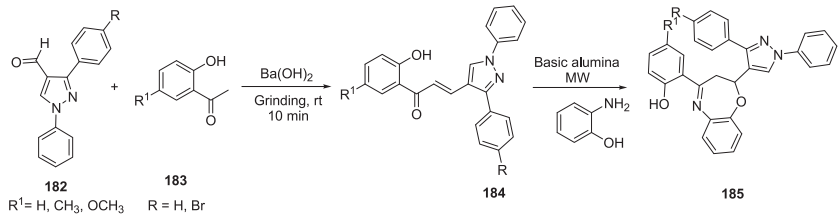
14.9 Use of heterogeneous catalysis

In recent years, heterogeneous catalysis is one of the fastest developing branches in chemistry and has received useful applications in various organic transformations due to several advantages over conventional homogeneous catalysis. Specially, it is strongly connected to popular environment-related applications. Several solid acid catalysts [151–153] such as Amberlyst [154], solid-supported fluoroboric acid [155], polyaniline sulfate [156], polystyrene-supported sulfonic acids [157], sulfated zirconia [158], and silica [159] synchronize with other greener techniques such as MW, ultrasound, environmentally benign solvents, and solvent-free conditions. Many of these efforts have found applications in the medium ring–sized heterocycles such as oxepines, azepines, diazepines, oxazepines, and thiazepines and screened, evaluated with respect to yields, reaction time, reaction temperature, and ease of purification, reusability, toxicity, and other hazards for sustained applications.

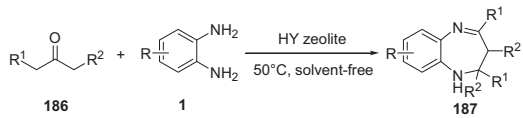
Pal and coworkers reported an efficient, metal-free, carbo-catalyzed (graphite oxide catalyzed) protocol for the synthesis of medicinally important benzodiazepines 181 (Scheme 14.53) at room temperature as well as under solvent-free heating condition [160]. Graphite oxide (GO) is an attractive candidate for environmentally benign heterogeneous catalysis because of flat monolayer carbon nonmaterial has captivated the organic chemist as graphine oxide contains



SCHEME 14.53 Synthesis of 1,5-benzodiazepines.



SCHEME 14.54 Synthesis of benzoxazepine.

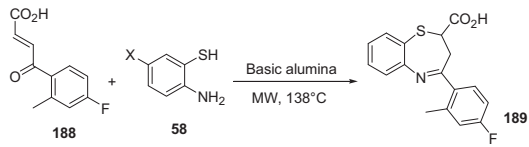


SCHEME 14.55 Synthesis of benzodiazepine derivative catalyzed by HY zeolite.

several functional groups including carbonyl (−C═O), hydroxyl (−OH), carboxyl (−COOH), and epoxy (−O−) groups [161]. A condensation reaction was proposed between aromatic diamine derivatives and α,β-unsaturated compound or ketone. The main role of catalyst GO increases the electrophilicity of the carbonyl through H-bonding which facilitates the attack of diammine to either the α,β-unsaturated compounds or ketones.

Very recently Ashok et al. described synthesis of benzoxazepine **185** (Scheme 14.54) derivative from pyrazole-chalcone **184** via a convenient protocol using basic alumina as solid support [162]. The synthesis was conducted at room temperature by grinding equimolar quantities of 2-hydroxy acetophenone derivative **183** and substituted pyrazole aldehyde **182** in the presence of $Ba(OH)_2$ for 10 min. Further, these pyrazole-chalcones **184** on thermal cyclization with 2-aminophenol in the presence of basic alumina under MW irradiation resulted benzoxazepines **185** in good yields within 20 min. The uniqueness of the methodology lies in its eco-friendly operation, with excellent yield.

Jeganathan and Pitchumani reported a solvent-free and HY zeolite–catalyzed synthesis of 1,5-benzodiazepines **187** (Scheme 14.55) from 1,2-diamines **1** and ketones [163] in high yields. The condensation reaction involves activation of ketone by HY zeolite via its Brønsted acidic sites,



SCHEME 14.56 Synthesis of benzothiaazepine derivative catalyzed by basic alumina.

followed by nucleophilic attack of the aromatic group of *o*-phenylenediamine to yield mono-imine. Subsequent proton removal and intramolecular cyclization promoted by HY zeolite give benzodiazepine **187**. The catalyst is recovered by filtration and reused six times without significant loss in its catalytic activity

A solvent-free, basic alumina-catalyzed synthesis of a variety of 8-substituted 2-carboxy-2,3-dihydro-1,5-benzothiazepines **189** (Scheme 14.56) was described under MW irradiation [164]. This one-step protocol delivered a good-to-excellent yield with a shorter reaction time compared to traditional method. Mechanistically, reaction proceeds in two steps involving first the formation of a Michael adduct as intermediate which then easily undergoes dehydrative cyclization to afford 1,5-benzothiazepines. The formation of the intermediate and the cyclized product was influenced by the basic aluminum catalyst.

14.10 Concluding remarks

From the foregoing discussions, it can be seen that medium ring–sized heterocyclic compounds find a wide range of applications in the arena of pharmaceuticals and medicinally important chemical entities. Synthetic activities addressing such scaffolds should continue toward the development of better ways. In particular, metal-mediated transformations have widened the scope of such compounds. Various multicomponent reactions have also shown new directions. All these developments have necessitated the use of greener technologies keeping in view the industrial regulations. Although many great advances have been made in the development of greener techniques which can efficiently compete with the conventional means, further advancements are necessary as many of such technologies are yet to complement many of the synthetic arsenals used to prepare such ring systems. This present overview is anticipated to boost future works in these directions.

References

[1] A.R. Katritzky, C. Ramsden, E. Scriven, R.J.K. Taylor (Eds.), Comprehensive Heterocyclic Chemistry, vols. 1–15, Elsevier, 2010.

[2] K.C. Majumdar, S.K. Chattopadhyay (Eds.), Heterocycles in Natural Product Synthesis, Wiley-VCH, 2011.

[3] J.H. Shah, R.M. Hindupur, H.N. Pati, Pharmacological and biological activities of benzazepines: an overview, Curr. Bioact. Compd. 11 (2015) 170–188.
[4] M. Driowya, A. Saber, H. Marzag, L. Demange, K. Bougrin, R. Benhida, Microwave-assisted syntheses of bioactive seven-membered, macro-sized heterocycles and their fused derivatives, Molecules 21 (2016) 1032.
[5] B. Amann, A. Sterr, R. Mergl, S. Dittmann, F. Seemüller, M. Dobmeier, M. Orth, M. Schaefer, H. Grunze, Zotepine loading in acute and severely manic patients: a pilot study, Bipolar Disorders 7 (2005) 471–476.
[6] T. Nabeshima, K. Matsuno, H. Kamei, T. Kameyama, The interaction of eptazocine, a novel analgesic, with opioid receptors, Res. Commun. Chem. Pathol. Pharmacol. 48 (1985) 173–181.
[7] E.H. Chartoff, M. Mavrikaki, Sex differences in kappa opioid receptor function and their potential impact on addiction, Front. Neurosci. 9 (2015) 466.
[8] T. Roehrs, F. Zorick, N. Lord, G.L. Koshorek, T. Roth, Dose-related effects of estazolam on sleep of patients with insomnia, J. Clin. Psychopharmacol. 3 (1983) 152–156.
[9] B.M. Smith, et al., Discovery and structure–activity relationship of (1*R*)-8-chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-3-benzazepine (lorcaserin), a selective serotonin 5-HT_{2C} receptor agonist for the treatment of obesity, J. Med. Chem. 51 (2008) 305–313.
[10] (a) K.P. Bøgesø, T. Liljefors, J. Arnt, J. Hyttel, H. Pedersen, Octoclothepin enantiomers. A reinvestigation of their biochemical and pharmacological activity in relation to a new receptor-interaction model for dopamine D-2 receptor antagonists, J. Med. Chem. 34 (1991) 2023–2030.
(b) R. All'Olio, A. Vaccheri, N. Montanaro, Reduced head-twitch response to quipazine of rats previously treated with methiothepin: possible involvement of dopaminergic system, Pharmacol. Biochem. Behav. 23 (1985) 43–48.
[11] S.E. Shoaf, M.V. Elizari, Z. Wang, K. Sekar, L.R. Grinfield, N.A. Barbagelata, J. Lerman, S.L. Bramer, J. Trongé, C. Orlandi, J. Cardiovasc. Pharmacol. Ther. 10 (2014) 165–171.
[12] D.J. Greenblatt, E. Woo, M.D. Allen, P.J. Orsulak, R.I. Shader, Rapid recovery from massive diazepam overdose, J. Am. Med. Assoc. 240 (1978) 1872.
[13] T. Roth, E.I. Tietz, M. Kramer, M. Kaffeman, The effect of a single dose of quazepam (Sch-16134) on the sleep of chronic insomniacs, J. Int. Med. Res. 7 (1979) 583.
[14] J. Fischer, C. Robin Ganellin, Analogue-Based Drug Discovery, John Wiley & Sons, 2006, p. 469.
[15] W.C. Liao, O. Vesterqvist, C. Delaney, M. Jemal, I. Ferreira, N. Ford, B. Swanson, H. Uderman, Pharmacokinetics and pharmacodynamics of the vasopeptidase inhibitor, omapatrilat in healthy subjects, Br. J. Clin. Pharmacol. 56 (2003) 395–406.
[16] G. Seminara, V. Trassari, N. Prestifilippo, R. Chiavetta, C. Calandra, Atypical tricyclic neuroleptics for treatment of schizophrenia. Clothiapine and clozapine, Minerva Psichiatr. 34 (1993) 95–99.
[17] C. Pignier, et al., Selective inhibition of persistent sodium current by F 15845 prevents ischaemia-induced arrhythmias, Br. J. Pharmacol. 161 (2010) 79–91.
[18] D. Podzamczer, E. Ferrer, E. Consiglio, A randomized clinical trial comparing nelfinavir or nevirapine associated to zidovudine/lamivudine in HIV-infected naive patients (the combine study), Antiviral Ther. 7 (2002) 81–90.
[19] J.T. Callaghan, R.F. Bergstrom, L.R. Ptak, et al., Olanzapine: pharmacokinetic and pharmacodynamic profile, Clin. Pharmacokinet. 37 (1999) 177–193.
[20] D.B. Rye, D.L. Bliwise, K. Parker, L.M. Trotti, P. Saini, J. Fairley, A. Freeman, P.S. Garcia, M.J. Owens, J.C. Ritchie, A. Jenkins, Modulation of vigilance in the primary

hypersomnias by endogenous enhancement of GABAA receptors, Sci. Transl. Med. 4 (2017) 161.

[21] K.V. Patel, A.V. Aspesi, K.E. Evoy, Suvorexant: a dual orexin receptor antagonist for the treatment of sleep onset and sleep maintenance insomnia, Ann. Pharmacother. 49 (2015) 477–483.

[22] P.C. Waldemeier, A.A. Boulton, A.R. Cools, et al., Neurorescuing effects of the GAPDH ligand CGP 34668, J. Neural Transm. Suppl. 60 (2000) 197–214.

[23] Y. Nagai, A. Irie, H. Nakamura, K. Hino, H. Uno, H. Nishimura, Nonsteroidal antiinflammatory agents. 1. 10,11-Dihydro-11-oxodibenz[*b*,*f*]oxepinacetic acids and related compounds, J. Med. Chem. 25 (1982) 1065.

[24] H.A. Heck, S.E. Buttrill Jr, N.W. Flynn, R.L. Dyer, M. Anbar, T. Cairns, S. Dighe, B.E. Cabana, Bioavailability of imipramine tablets relative to a stable isotope-labelled internal standard: increasing the power of bioavailability test, J. Pharm. Biopharm. 7 (1979) 233–248.

[25] [a] P.A. Evans, A.B. Holmes, Medium ring nitrogen heterocycles, Tetrahedron 47 (1991) 9131–9166.

[b] G.A. Molander, Diverse methods for medium ring synthesis, Acc. Chem. Res. 31 (1998) 603–609.

[c] J.A. Hoberg, Synthesis of seven-membered oxacycles, Tetrahedron 54 (1998) 12631–12670.

[d] L. Yet, Free radicals in the synthesis of medium-sized rings, Tetrahedron 55 (1999) 9349–9403.

[e] R. Olivera, R. Sanmartin, F. Churruca, E. Dominguez, Dibenzo[*b*,*f*]oxepines: synthesis and applications. A review, Org. Prep. Proced. Int. 36 (2004) 297–330.

[f] A. Sharma, P. Appukkuttan, E. Van der Eicken, Microwave-assisted synthesis of medium-sized heterocycles, Chem. Commun. 48 (2012) 1623–1637.

[26] S.K. Chattopadhyay, Green synthetic approaches for medium ring-sized heterocycles of biological interest, in: G. Brahmachari (Ed.), Green Synthetic Approaches for Biologically Relevant Heterocycles, Elsevier, 2014, Chapter 11, 1st edition, pp. 291–315.

[27] E.L. Smith, A.P. Abbott, K.S. Ryder, Deep eutectic solvents (DESs) and their applications, Chem. Rev. 114 (2014) 11060.

[28] R. Yusof, E. Abdulmalek, K. Sirat, M.B.A. Rahman, Tetrabutylammonium bromide (TBABr)-based deep eutectic solvents (DESs) and their physical properties, Molecules 19 (2014) 8011.

[29] D.V. Wagle, H. Zhao, G.A. Baker, Deep eutectic solvents: sustainable media for nanoscale and functional materials, Acc. Chem. Res. 47 (2014) 2299.

[30] A. Shaabani, E.S. Hooshmand, T.M. Nazeri, R. Afshari, S. Ghasemi, Deep eutectic solvent as a highly efficient reaction media for the one-pot synthesis of benzo-fused seven-membered heterocycles, Tetrahedron Lett. 57 (2016) 3727.

[31] A. Dandia, R. Singh, J. Soshi, S. Maheswari, Green and chemoselective synthesis of pyrazolo[3,4-*e*][1,4]thiazepines and evaluation of their anti-infective activities, Res. Chem. Intermed. 41 (2015) 4213.

[32] M. Ghandi, N. Zarezadeh, A. Abbasi, One-pot tandem Ugi-4CR/SNSNAr approach to highly functionalized quino[2,3-*b*][1,5]benzoxazepines, Mol. Diversity 20 (2016) 483.

[33] V.G. More, M.B. Bhanage, Ru-catalyzed asymmetric transfer hydrogenation of substituted dibenzo[*b*,*f*][1,4]oxazepines in water, Org. Biomol. Chem. 15 (2017) 5263.

[34] Y. Zhao, C. Wang, Y. Hu, B. Wan, Brønsted acid-catalyzed formal [5 + 2 + 1] cycloaddition of ynamides and isoxazoles with water: access to oxygen-bridged tetrahydro-1,4-oxazepines, Chem. Commun. 54 (2018) 3963.

[35] C.S. Radatz, R.B. Silva, G. Perin, E.J. Lenardão, R.G. Jacob, D. Alves, Catalyst-free synthesis of benzodiazepines and benzimidazoles using glycerol as recyclable solvent, Tetrahedron Lett. 52 (2011) 4132.

[36] L.-Z. Wang, X.-Q. Li, Y.-S. An, 1,5-Benzodiazepine derivatives as potential antimicrobial agents: design, synthesis, biological evaluation, and structure−activity relationships, Org. Biomol. Chem. 13 (2015) 5497.

[37] Y.-W. Sun, Y.-M. Bei, L.-Z. Wang, A catalyst-free four-component domino reaction for the synthesis of functionalized 3-acyl-1,5-benzodiazepines, Org. Biomol. Chem. 17 (2019) 930.

[38] A. Solan, B. Nişanci, M. Belcher, J. Young, C. Schäfer, A.K. Wheeler, B. Török, R. Dembinski, Catalyst-free chemo-/regio-/stereo-selective amination of alk-3-ynones. Synthesis of 1,5-benzodiazepines and 3-amino-2-alkenones, Green Chem. 16 (2014) 1120.

[39] J.N. Sangshetti, R.S. Chouthe, M.R. Jadhav, N.S. Sakle, A. Chabukswar, I. Gonjari, S. Darandale, D B, Green synthesis and anxiolytic activity of some new dibenz-[1,4] diazepine-1-one analogues, Arab. J. Chem. 10 (2017) 1365.

[40] R.V. Devi, A.M. Garande, D.K. Maity, P.K. Bhate, A. Serendipitous, Synthesis of 11a-hydroxy-11,11a-dihydrobenzo[*e*]indeno[2,1-*b*][1,4]diazepine-10,12-dione derivatives by condensation of 2-aminobenzamides with ninhydrin in water, J. Org. Chem. 81 (2016) 1689.

[41] R. Kange, V. Kalalawa, S. Niwadange, R. Gutte, D. Munde, Synthesis of 1,5-benzodiazepine derivatives using sulphated tin oxide as solid super acid catalyst, Int. J. Res. Anal. Res. 6 (2019) 492.

[42] A.J. Coggins, D.A. Tocher, M.W. Powner, One-step protecting-group-free synthesis of azepinomycin in water, Org. Biomol. Chem. 13 (2015) 3378.

[43] D.R. Kommidi, R. Pagadala, M. Varkolu, N.A. Koorbanally, B.J. Moodley, New route for the synthesis of thiazolidine 2,4dione azepine derivatives, Het. Chem. 54 (2016).

[44] S.K. Maddili, R. Chowrasia, V.K. Kannekanti, H. Gandham, 1,3-Di-*n*-butylimidazolium tribromide [BBim]Br_3: an efficient recyclable catalyst mediated synthesis of N-substituted azepines and their biological evaluation-interaction study with human serum albumin, J. Photobiol. B Biol. 178 (2018) 101.

[45] R. Sakirolla, K. Tadiparthi, M. Yaeghoobi, N. Rahman, Di-cationic ionic liquid catalyzed synthesis of 1,5-benzothiazepines, Asian J. Chem. 30 (2018) 107.

[46] H. Naeimi, H. Foroughi, Efficient, environmentally benign, one-pot procedure for thesynthesis of 1,5-benzodiazepine derivatives using *N*-methyl-2-pyrrolidonium hydrogen sulphate as an ionic liquid catalyst under solvent-free conditions, Chin. J. Catal. 36 (2015) 734.

[47] M. Herranz, L. Sanchez, N. Martin, Tetrathiafulvalene: a paradigmatic electron donor molecule, Phosphorus, Sulfur Silicon Relat. Elem. 180 (2005) 1133.

[48] B. Das, S. Srivastava, J. Sarvanan, S. Mohan, Synthesis and antifungal screening of some novel sulfur containing heterocyclic compounds, Asian J. Chem. 19 (2007) 4118.

[49] T. Shigetomi, H. Soejima, Y. Nibu, K. Shioji, K. Okuma, Y. Yokomori, Synthesis and reaction of α-dithiolactone, Chem. Eur. J. 12 (2006) 7742.

[50] L. Yet, Metal-mediated synthesis of medium-sized rings, Chem. Rev. 100 (2000) 2963.

[51] A. Vasudevan, P.S. Tseng, S.W. Djuric, A post aza Baylis−Hillman/Heck coupling approach towards the synthesis of constrained scaffolds, Tetrahedron Lett. 47 (2006) 8591.

[52] D. Dallinger, C.O. Kappe, Microwave-assisted synthesis in water as solvent, Chem. Rev. 107 (2007) 2563.

[53] S.-J. Tu, X.-D. Cao, W.-J. Hao, X.-H. Zhang, S. Yan, S.-S. Wu, Z.-G. Han, F. Shi, An efficient and chemoselective synthesis of benzo[*e*][1,4]thiazepin-2(1*H*, 3*H*, 5*H*)-ones *via* a microwave-assisted multi-component reaction in water, Org. Biomol. Chem. 7 (2009) 557.

[54] D. Vyawahare, M. Ghodke, A.P. Nikalje, Green synthesis and pharmacological screening of novel 1,5-benzothiazepines as CNS agents, Int. J. Pharm. Pharm. Sci. 2 (2010) 27.
[55] B. Willy, T.J. Muller, Three-component synthesis of benzo[*b*][1,5]thiazepines via coupling–addition–cyclocondensation sequence, Mol. Diversity 14 (2010) 443.
[56] J.S. Yadav, Y.K. Srivastava, Importance of microwave reactions in the synthesis of novel benzimidazole derivatives, Pharm. Lett. 3 (2011) 284.
[57] A.P. Nikalje, D. Vyawahare, Facile green synthesis of 2,4-substituted-2,3-dihydro-1,5 benzothiazepine derivatives as novel anticonvulsant and central nervous system (CNS) depressant agents, Afr. J. Pure Appl. Chem. 5 (2011) 422.
[58] D. Plouffe, A. Brinker, C. McNamara, K. Henson, N. Kato, K. Kuhen, A. Nagle, F. Adrian, J.T. Matzen, P. Anderson, T. Nam, N.S. Gray, A. Chatterjee, J. Janes, S.F. Yan, R. Trager, J.S. Caldwell, P.G. Schultz, Y. Zhou, E.A. Winzeler, *In silico* activity profiling reveals the mechanism of action of antimalarials discovered in a high-throughput screen, Proc. Natl. Acad. Sci. U.S.A. 105 (2008) 9059.
[59] K. Saruta, T. Ogiku, K. Fukase, Traceless solid-phase synthesis of multiple sulfonamide-containing cyclic sulfides exploiting microwave irradiation, Tetrahedron Lett. 50 (2009) 4364.
[60] N. Božinović, I. Novaković, S.K. Rajačić, I.M. Opsenica, A. Šolajab, Synthesis and antimicrobial activity of azepine and thiepine derivatives, J. Serb. Chem. Soc. 80 (2015) 839.
[61] C.S. Morrison, J.B. Lampe, T.C. Kolodziejczyk, R.J. Cavazos, R.A. Petros, Rapid, quantitative, solvent-free synthesis of medium-ring diaza heterocycles from diketene–acetone adduct and diamines, Tetrahedron Lett. 55 (2014) 6547–6549.
[62] F. De Moliner, M. Bigatti, C. De Rosas, L. Banfi, R. Riva, A. Basso, Synthesis of triazolo-fused benzoxazepines and benzoxazepinones via Passerini reactions followed by 1,3-dipolar cycloadditions, Mol. Diversity 18 (2014) 473–482.
[63] M.A. Ibrahim, S.S. Panda, A.A. Oliferenko, P.V. Oliferenko, A.S. Girgis, M. Elagawany, et al., Macrocyclic peptidomimetics with antimicrobial activity: synthesis, bioassay, and molecular modeling studies, Org. Biomol. Chem. 13 (2015) 9492–9503.
[64] S.S. Kotalwar, A.D. Kale, R.B. Kohire, V.B. Jagrut, Microwave assisted synthesis of 1,5-benzothiazepines using greener reaction medium, Asian J. Chem 31 (2019) 993.
[65] J. Shi, J. Wu, C. Cui, W.M. Dai, Microwave-assisted intramolecular Ullmann diaryl etherification as the post-Ugi annulation for generation of dibenz[*b*,*f*][1,4]oxazepine scaffold, J. Org. Chem. 81 (2016) 10392.
[66] M. Avnon, et al., Effectiveness of clozapine in hospitalised people with chronic neuroleptic resistant schizophrenia, Br. J. Psychiatry 167 (1996) 760–764.
[67] N. Saadatjoo, M. Javaheria, N. Saemian, M. Aminic, Synthesis of a carbon-14 analog of 8-chloro-11-(4-methyl-1-piperazinyl)-11-[^{14}C]-5*H*-dibenzo[*b*,*e*][1,4]diazepine (clozapine) using microwave irradiation, Radiochemistry 58 (2016) 423.
[68] (a) J.-T. Li, W.-Z. Yang, S.-X. Wang, S.-H. Li, T.-S. Li, Improved synthesis of chalcones under ultrasound irradiation, Ultrason. Sonochem. 9 (2002) 237.
(b) F.L. Ansari, F. Iftikhar, B. Mirza, M. Baseer, U. Rashid, Solid-phase synthesis and biological evaluation of a parallel library of 2,3-dihydro-1,5-benzothiazepines, Bioorg. Med. Chem. 16 (2008) 7691–7697.
[69] L. Zare, N.O. Mahmoodi, A. Yahyazadeh, M. Nikpassand, Ultrasound-promoted regio and chemoselective synthesis of pyridazinones and phthalazinones catalyzed by ionic liquid [bmim]Br/$AlCl_3$, Ultrason. Sonochem. 19 (2012) 740.
[70] Y. Zou, H. Wu, Y. Hu, H. Liu, X. Zhao, H.L. Ji, D.Q. Shi, A novel and environment-friendly method for preparing dihydropyrano[2,3-*c*]pyrazoles in water under ultrasound irradiation, Ultrason. Sonochem. 18 (2011) 708.

[71] (a) G.H. Mahdavinia, S. Rostamizadeh, A.M. Amani, Z. Emdadi, Ultrasound-promoted greener synthesis of aryl-14-*H*-dibenzo[*a*,*j*]xanthenes catalyzed by $NH_4H_2PO_4/SiO_2$ in water, Ultrason. Sonochem. 16 (2009) 7.
(b) J. Trilleras, E. Polo, J. Quiroga, J. Cobo, M. Nogueras, Ultrasonics promoted synthesis of 5-(pyrazol-4-yl)-4,5-dihydropyrazoles derivatives, Appl. Sci. 3 (2013) 457–468.

[72] M. Nuchter, B. Ondruschka, A. Jungnickel, U. Muller, Organic processes initiated by non-classical energy sources, J. Phys. Org. Chem. 13 (2000) 579.

[73] S.J. Ji, Z.L. Shen, D.G. Gu, X.Y. Huang, Ultrasound-promoted alkynylation of ethynylbenzene to ketones under solvent-free condition, Ultrason. Sonochem. 12 (2005) 161.

[74] J.T. Li, Y. Yin, L. Li, M.X. Sun, A convenient and efficient protocol for the synthesis of 5-aryl-1,3-diphenylpyrazole catalyzed by hydrochloric acid under ultrasound irradiation, Ultrason. Sonochem. 17 (2010) 11.

[75] L. Pizzuti, P.L.G. Martins, B.A. Ribeiro, F.H. Quina, E. Pinto, A.F.C. Flores, D. Venzke, C.M.P. Pereira, Efficient sonochemical synthesis of novel 3,5-diaryl-4,5-dihydro-1*H*-pyrazole-1-carboximidamides, Ultrason. Sonochem. 17 (2010) 34.

[76] R. Juarez, P. Concepcion, A. Corma, H. Garcia, Ceria nanoparticles as heterogeneous catalyst for CO_2 fixation by ω-aminoalcohols, Chem. Commun. 46 (2010) 4181.

[77] G. Cravotto, P. Cintas, Power ultrasound in organic synthesis: moving cavitational chemistry from academia to innovative and large-scale applications, Chem. Soc. Rev. 35 (2006) 180.

[78] Y. Jiang, X. Chen, L. Qu, J. Wang, J. Yuan, S. Chen, X. Li, C. Qu, Ultrasonic-assisted synthesis of chrysin derivatives linked with 1,2,3-triazoles by 1,3-dipolar cycloaddition reaction, Ultrason. Sonochem. 18 (2011) 527.

[79] M.A. Martings, C.M. Pereira, W.M.S. Cunico, F.A. Rosa, R.L. Peres, P. Machado, N. Zanatta, H.G. Bonacorso, Ultrasound promoted synthesis of 5-hydroxy-5-trihalomethyl-4,5-dihydroisoxazoles and β-enamino trihalomethyl ketones in water, Ultrason. Sonochem. 13 (2006) 364.

[80] S.J. Ji, S.Y. Wang, An expeditious synthesis of β-indolylketones catalyzed by *p*-toluenesulfonic acid (PTSA) using ultrasonic irradiation, Ultrason. Sonochem. 12 (2005) 339.

[81] (a) Z.L. Shen, S.J. Ji, S.Y. Wang, X.F. Zeng, A novel base-promoted synthesis of β-indolylketones via a three-component condensation under ultrasonic irradiation, Tetrahedron 61 (2005) 10552.
(b) E. Ruiz, H. Rodriguez, J. Coro, E. Salfran, M. Suarez, R. Martinez-Alvarez, N. Martin, Ultrasound-assisted one-pot, four component synthesis of 4-aryl 3,4-dihydropyridone derivatives, Ultrason. Sonochem. 18 (2011) 32.

[82] H. Xu, W.M. Liao, H.F. Li, A mild and efficient ultrasound-assisted synthesis of diaryl ethers without any catalyst, Ultrason. Sonochem. 14 (2007) 779.

[83] (a) K.P. Guzen, A.S. Guarezemini, A.T.G. Orfao, R. Cella, C.M.P. Pereira, P.H.A. Stefani, Eco-friendly synthesis of imines by ultrasound irradiation, Tetrahedron Lett. 48 (2007) 1845.
(b) V.S.V. Satyanarayana, A. Sivakumar, Ultrasound-assisted synthesis of 2,5-dimethyl-N-substituted pyrroles catalyzed by uranyl nitrate hexahydrate, Ultrason. Sonochem. 18 (2011) 917–1922.

[84] T.S. Saleh, N.M.A. El-Rahman, A.A. Elkateb, N.O. Shaker, N.A. Mahmoud, S.A. Gabal, Ultrasound promoted synthesis of some novel fused pyrans, Ultrason. Sonochem. 19 (2012) 491.

[85] D. Nagargoje, P. Mandhane, S. Shingote, P. Badadhe, C. Gill, Ultrasound assisted one pot synthesis of imidazole derivatives using diethyl bromophosphate as an oxidant, Ultrason. Sonochem. 19 (2012) 94.
[86] M. Dabiri, Z. Noroozi Tisseh, M. Bahramnejad, A. Bazgir, Sonochemical multicomponent synthesis of spirooxindoles, Ultrason. Sonochem. 18 (2011) 1153.
[87] N.M. Abdel-Rahman, T.S. Saleh, M.F. Mady, Ultrasound assisted synthesis of some new 1,3,4-thiadiazole and bi(1,3,4-thiadiazole) derivatives incorporating pyrazolone moiety, Ultrason. Sonochem. 16 (2009) 70.
[88] Z.H. Zhang, J.J. Li, T.S. Li, Ultrasound-assisted synthesis of pyrroles catalyzed by zirconium chloride under solvent-free conditions, Ultrason. Sonochem. 15 (2008) 673.
[89] A. Bazgir, S. Ahadi, R. Ghahremanzadeh, H.R. Khavasi, P. Mirzaei, Ultrasound-assisted one-pot, three-component synthesis of spiro[indoline-3,4′-pyrazolo[3,4-*b*]pyridine]-2,6′(1′*H*)-diones in water, Ultrason. Sonochem. 17 (2010) 447.
[90] A.V. Chate, R.S. Joshi, P.G. Mandhane, C.H. Gill, An improved procedure for the synthesis of 1,5-benzothiazepines using ceric ammonium nitrate (CAN), J. Korean Chem. Soc. 55 (2011) 776.
[91] K.A.M. El-Bayouki, Benzo[1,5]thiazepine: synthesis, reactions, spectroscopy, and applications, Org. Chem. Int. 2013 (2013) 71.
[92] P.V. Shinde, B.B. Shingate, M.S. Shingare, Bull. Korean Chem. Soc. 32 (2011) 1179.
[93] M.S.F. Lie Ken Jie, P. Kalluri, Synthesis of pyridazine fatty ester derivatives in water: a sonochemical approach, J. Chem. Soc. Perkin Trans. 1 (1995) 1205.
[94] M.S.F. Lie Ken Jie, P. Kalluri, Synthesis of pyridazine fatty ester derivatives in water: a sonochemical approach, J. Chem. Soc. Perkin Trans. 1 (1997) 3485.
[95] H.P. Jensen, K.B. Sharpless, Improved procedure for the direct oxidation of olefins to alpha.-diketones by potassium permanganate in acetic anhydride, J. Org. Chem. 39 (1974) 2314.
[96] D. Lloyd, R.H. McDougall, D.R. Marshall, Diazepines. Part III. Some benzodiazepines, J. Chem. Soc. (1966) 780.
[97] D. Gopal, D.V. Nadkarni, L.M. Sayre, A novel monoalkylation of symmetrical α-diones, Tetrahedron Lett. 39 (1998) 1877.
[98] G.W.H. Potter, M.W. Coleman, A.M. Monro, Spectral properties and ring conformation of some novel 2,3-dihydro-1*H*-1,4-diazepinium cations, J. Heterocycl. Chem. 12 (1975) 611.
[99] S.F. Marcel, L.K. Jie, M.M.L. Lau, P. Kalluri, Lipids 36 (2001) 2.
[100] H. Wolf, The Schmidt reaction, Org. React. 3 (1946) 345.
[101] A.H. Balnt, The Beckmann rearrangement, Chem. Rev. 12 (1933) 215.
[102] V. Padmavarthi, R.T.V. Reddy, K.A. Reddy, A. Padamja, D.B. Reddy, A study on the reactivity of 1,3-dimethyl-2,6-diphenyl-4-piperidone: synthesis of some novel heterocycles, Ind. J. Chem. 44B (2005) 2527.
[103] D.H.R. Barton, P. De Mayo, M. Shafiq, Photochemical transformations. Part II. The constitution of lumisantonin, J. Chem. Soc. (1958) 140–145.
[104] H.E. Zimmerman, Five decades of mechanistic and exploratory organic photochemistry, Pure Appl. Chem. 78 (2006) 2193–2203.
[105] A. Albini, M. Fagnoni, Green chemistry and photochemistry were born at the same time, Green Chem. 6 (2004) 1.
[106] A. Albini, M. Fagnoni, M. Mella, Environment-friendly organic synthesis. The photochemical approach, Pure Appl. Chem. 72 (2000) 1321.
[107] P.I. Dalko, L. Moisan, In the Golden Age of organocatalysis, Angew. Chem. Int. Ed. Engl. 43 (2004) 5138.

[108] B. List, Proline-catalyzed asymmetric reactions, Tetrahedron 58 (2002) 5573.
[109] K.C. Nicolaou, D. Vourloumis, N. Winssinger, P.S. Baran, The art and science of total synthesis at the dawn of the twenty-first century, Angew. Chem. Int. Ed. 39 (2000) 44.
[110] (a) N. Kaur, Palladium catalysts: synthesis of five-membered *N*-heterocycles fused with other heterocycles, Catal. Rev. 57 (2015) 1.
(b) N. Kaur, D. Kishore, Microwave-assisted synthesis of six-membered *O*,*O*-heterocycles, Synth. Commun. 44 (2014) 3082.
(c) P.A. Wender, M.P. Croatt, B. Witulski, New reactions and step economy: the total synthesis of (±)-salsolene oxide based on the type II transition metal-catalyzed intramolecular [4 + 4] cycloaddition, Tetredron 62 (2006) 7505.
(e) S. Singh, P. Kaur, IPL visualization and prediction using HBase, Curr. Organocatal. 122 (2017) 910.
(d) N. Kaur, Perspectives of ionic liquids applications for the synthesis of five- and six-membered *O*,*N*-heterocycles, Synth. Commun. 48 (2018) 473.
[111] K. Lamara, R.K. Smalley, 3*H*-Azepines and related systems. Part 4. Preparation of 3*H*-azepin-2-ones and 6*H*-azepino[2,1-*b*]quinazolin-12-ones by photo-induced ring expansions of aryl azides, Tetrahedron 47 (1991) 2277.
[112] F.R. Bou-Hamdan, F. Levesque, A.G. O'Brien, P.H. Seeberger, Continuous flow photolysis of aryl azides: preparation of 3*H*-azepinones, Beilstein J. Org. Chem. 7 (2011) 1124.
[113] J.M. Nuss, The photochemistry of dienes and polyenes: application to the synthesis of complex molecules, The Chemistry of Dienes and Polyenes, vol. 1, John Wiley & Sons, 1999, p. 263.
[114] D.K. Winter, A. Drouin, J. Lessard, C. Spino, Photochemical rearrangement of *N*-chlorolactams: a route to N-heterocycles through concerted ring contraction, J. Org. Chem. 75 (2010) 2610.
[115] P.H. Mazzocchi, S. Minamikawa, P. Wilson, Competitive photochemical ($\sigma 2 + \pi 2$) addition and electron transfer in the *N*-methylphthalimide-alkene system, J. Org. Chem. 50 (1985) 2681.
[116] (a) K. Maruyama, Y. Kubo, Photochemistry of phthalimides with olefins. Solvent-incorporated addition vs. cycloaddition to imide C(=O)-N bond accompanying ring enlargement, J. Org. Chem. 5 (1985) 1426.
(b) K.I. Booker-Milburn, C.E. Anson, C. Clissold, N.J. Costin, R.F. Dainty, M. Murray, D. Patel, A. Sharpe, Intramolecular photocycloaddition of *N*-alkenyl substituted maleimides: a potential tool for the rapid construction of perhydroazaazulene alkaloids, Eur. J. Org. Chem. (2001) 1473.
[117] R.A. Pilli, M.C. Ferreira de Oliveira, Recent progress in the chemistry of the stemona alkaloids, Nat. Prod. Rep. 17 (2000) 117.
[118] K.I. Booker-Milburn, P. Hirst, J.P.H. Charmant, L.H. Taylor, A. Rapid, Stereocontrolled entry to the ABCD tetracyclic core of neotuberostemonine, Angew. Chem. Int. Ed. Engl. 42 (2003) 1642.
[119] M.D. Lainchbury, M.I. Medley, P.M. Taylor, P. Hirst, W. Dohle, K.I. Booker-Milburn, A protecting group free synthesis of (±)-neostenine via the [5 + 2] photocycloaddition of maleimides, J. Org. Chem. 73 (2008) 6497.
[120] B.D.A. Hook, W. Dohle, P.R. Hirst, M. Pickworth, M.B. Berry, K.I. Booker-Milburn, A practical flow reactor for continuous organic photochemistry, J. Org. Chem. 70 (2005) 7558.
[121] T. Bach, J.P. Hehn, Photochemical reactions as key steps in natural product synthesis, Angew. Chem. Int. Ed. Engl. 50 (2011) 1000.

[122] M. Machida, H. Takechi, Y. Shishido, Y. Kanaoka, Photochemical synthesis of multicyclic fused imidazolidines, hydropyrazines, and hydro-1,4-diazepines, Synthesis 1982 (1982) 1078.
[123] H. Takechi, S. Tateuchi(Nee Oyadomari), M. Machida, Y. Nishibata, K. Aoe, Y. Sato, Y. Kanaoka, Photoreactions of succinimides with an *N*-acyl group in the side chain. Synthesis and stereochemistry of tricyclic pyrrolo(1,2-*a*)pyrazine ring systems, Chem. Pharm. Bull. 34 (1986) 3142.
[124] (a) N. Hoffmann, Photochemical reactions as key steps in organic synthesis, Chem. Rev. 108 (2008) 1052.
(b) A. Reisinger, P.V. Bernhardt, C. Wentrup, Synthesis of 1,3-Diazepines and ring contraction to cyanopyrroles, Org. Biomol. Chem. 2 (2004) 246.
[125] A. Reisinger, R. Koch, P.V. Bernhardt, C. Wentrup, 1*H*-1,3-Diazepines, 5*H*-1,3-diazepines, 1,3-diazepinones, and 2,4-diazabicyclo[3.2.0]heptenes, Org. Biomol. Chem. 2 (2004) 1227.
[126] F. Peyrane, M. Cesario, P. Clivio, Photochemical ring expansion of 4-azidouracil: a route to 5*H*-1,3,5-triazepin-2,4-dione in the nucleoside series, J. Org. Chem. 71 (2006) 1742.
[127] R.G. Brinson, S.C. Hubbard, D.R. Zuidema, P.B. Jones, Two new anthraquinone photoreactions, J. Photochem. Photobiol. A 175 (2005) 118.
[128] U. Streit, C.G. Bochet, The arene–alkene photocycloaddition, Beilstein J. Org. Chem. 7 (2011) 525.
[129] G.P. Kalena, P. Pradhan, A. Banerji, A novel intramolecular 1,2-arene-alkene photocycloaddition, Tetrahedron Lett. 33 (1992) 7775.
[130] P. Chen, Y. Chen, P.J. Carroll, S. McNSieburth, Novel reaction pathways for 2-pyridone [4 + 4] photoadducts, Org. Lett. 8 (2006) 3367.
[131] D.D. Wu, L. Wang, K. Xu, J. Song, H.K. Fun, J.-H. Xu, Y. Zhang, A facile and highly atom-economic approach to biaryl-containing medium-ring bislactones, Chem. Commun. 48 (2012) 1168.
[132] C. Huang, M. Zheng, J. Xu, Y. Zhang, Photo-induced cycloaddition reactions of α-diketones and transformations of the photocycloadducts, Molecules 18 (2013) 2942.
[133] T.R. Hoye, W.S. Richardson, A short, oxetane-based synthesis of (. + -.)-sarracenin, J. Org. Chem. 54 (1989) 688.
[134] G. Kaupp, M.R. Naimi-Jamal, H. Ren, H. Zoz, in: G. Cao, F. Delogu, R. Orru (Eds.), Advanced Technologies Based on Self-Propagating and Mechanochemical Reactions for Environmental Protection, *Research Signpost*, Kerala, 2003, pp. 83–100.
[135] H. Ren, H. Zoz, G. Kaupp, M.R. Naimi-Jamal, Adv. Powder Metall. Part. Mater. (2003) 216–222.
[136] H. Zoz, G. Kaupp, H. Ren, K. Goepel, M.R. Naimi-Jamal, Metall. Mater. Trans. 59 (2005) 293–296.
[137] A. Bakhshai, R. Pragani, L. Takacs, Metall. Mater. Trans. A 33A (2002) 3521–3526.
[138] G. Brahmachari, B. Banerjee, Facile and one-pot access of 3,3-bis (indol-3-yl) indolin-2-ones and 2,2-bis(indol-3-yl) acenaphthylen-1 (2*H*)-one derivatives via an eco-friendly pseudo-multicomponent reaction at room temperature using sulfamic acid as an organocatalyst, ACS Sustain. Chem. Eng. 2 (2014) 2802–2812.
[139] W. Foye, Principal di Chemico Farmaceutica, Piccin, Padova, 1991, p. 416.
[140] S. Mashkouri, M.R. Naimi-Jamal, Mechanochemical solvent-free and catalyst-free one-pot synthesis of pyrano [2,3-*d*] pyrimidine-2,4 (1*H*,3*H*)-diones with quantitative yields, Molecules 14 (2009) 474–479.
[141] A.D. McNaught, A. Wilkinson, Compendium of Chemical Terminology; IUPAC Recommendations, IUPAC: Zürich, Switzerland, 1997.

[142] A. Stolle, T. Szuppa, S.E. Leonhardt, B. Ondruschka, Ball milling in organic synthesis: solutions and challenges, Chem. Soc. Rev. 40 (2011) 2317–2329.
[143] M. Ould M'hamed, Ball milling for heterocyclic compounds synthesis in green chemistry: a review, Synth. Commun. 45 (2015) 2511–2528.
[144] G.-W. Wang, Mechanochemical organic synthesis, Chem. Soc. Rev. 42 (2013) 7668–7700.
[145] D. Margetic, V. Štrukil, Mechanochemical Organic Synthesis, Elsevier, New York, NY, 2016.
[146] T. Friščíc, Supramolecular concepts and new techniques in mechanochemistry: cocrystals, cages, rotaxanes, open metal–organic frameworks, Chem. Soc. Rev. 41 (2012) 3493–3510.
[147] L. Carlier, M. Baron, A. Chamayou, G. Couarraze, Use of co-grinding as a solvent-free solid state method to synthesize dibenzophenazines, Tetrahedron Lett. 52 (2011) 4686–4689.
[148] I.T. Horváth, J. Rábai, Facile catalyst separation without water: fluorous biphase hydroformylation of olefins, Science 266 (1994) 72–75.
[149] [a] D.P. Curran, R. Ferritto, Y. Hua, Preparation of a fluorous benzyl protecting group and its use in fluorous synthesis approach to a disaccharide, Tetrahedron Lett. 39 (1998) 4937–4940.
[b] W. Zhang, D.P. Curran, Synthetic applications of fluorous solid-phase extraction (F-SPE), Tetrahedron 62 (2006) 11837–11865.
[c] V. Montanari, K. Kumar, Just add water: a new fluorous capping reagent for facile purification of peptides synthesized on the solid phase, J. Am. Chem. Soc. 126 (2004) 9528–9529.
[150] W.-B. Yi, C. Cai, Ytterbium perfluorooctanesulfonate–catalyzed synthesis of 1,5-benzodiazepine derivatives in fluorous solvents, Synth. Commun. 37 (2007) 3824.
[151] G. Ertl, H. Knzinger, J. Weitkamp (Eds.), Handbook of Heterogeneous Catalysis, Wiley-VCH Verlag GmbH, Weinheim, 1997.
[152] W. Ostwald, Definition der Katalyse, Z. Phys. Chem. 15 (1894) 705–706.
[153] For a review, see J.H. Clark, Solid acids for green chemistry, Acc. Chem. Res. 35 (2002) 791–797.
[154] S.A. Singh, S. Kabiraj, R.P. Khandare, S.P. Nalawade, K.B. Upar, S.V. Bhat, Amberlyst-15–catalyzed efficient cyclization of γ- and δ-unsaturated alcohols: green synthesis of oxygen heterocycles, Synth. Commun. 40 (2010) 74–80.
[155] B.P. Bandgar, A.V. Patil, O.S. Chavan, Silica supported fluoroboric acid as a novel, efficient and reusable catalyst for the synthesis of 1,5-benzodiazepines under solvent-free conditions, J. Mol. Catal. A. Chem. 256 (2006) 99–105.
[156] U. Srinivasa, Ch Srinivas, P. Narender, V. Jayathirtha Rao, S. Palaniappan, Polyaniline-sulfate salt as an efficient and reusable catalyst for the synthesis of 1,5-benzodiazepines and 2-phenyl benzimidazoles, Catal. Commun. 8 (2007) 107–110.
[157] V. Polshttiwar, R.S. Varma, Greener and rapid access to bio-active heterocycles: room temperature synthesis of pyrazoles and diazepines in aqueous medium, Tetrahedron Lett. 49 (2008) 397–400.
[158] B.M. Reddy, P.M. Sreekanth, An efficient synthesis of 1,5-benzodiazepine derivatives catalyzed by a solid superacid sulfated zirconia, Tetrahedron Lett. 44 (2003) 4447–4449.
[159] R.K. Saini, Y.C. Joshi, P. Joshi, Solvent-free synthesis of some 1,5-benzothiazepines and benzodiazepines and their antibacterial activity, Phosphorus, Sulfur Silicon Relat. Elem. 183 (2008) 2181–2190.

[160] R. Jamatia, A. Gupta, B. Dam, M. Saha, A.K. Pal, Graphite oxide a metal free highly efficient carbocatalyst for the synthesis of 1,5-benzodiazepines under room temperature and solvent free heating condition, Green Chem. 19 (2017) 1576.
[161] T. Szabo, E. Tombacz, E. Illes, I. Dekany, Enhanced acidity and pH-dependent surface charge characterization of successively oxidized graphite oxide, Carbon 44 (2006) 537.
[162] D. Ashok, G. Radhika, B.A. Rao, M. Sarasija, A. Jayashree, P. Sadanandam, Synthesis of benzoxazepine derivative from pyrazole-chalcone via a convenient protocol using basic alumina as solid support, J. Chil. Chem. Soc. 63 (2018) 3983.
[163] M. Jeganathan, K. Pitchumani, Solvent-free syntheses of 1,5-benzodiazepines using HY zeolite as a green solid acid catalyst, Sustain. Chem. Eng. 2 (2014) 1169.
[164] A. Dandia, M. Sati, A. Loupy, Dry-media one-pot syntheses of fluorinated-2,3-dihydro-1,5-benzothiazepines under microwave activation, Green Chem. 4 (2002) 599.

Advances in **Green and Sustainable Chemistry**

Green Synthetic Approaches for Biologically Relevant Heterocycles

Volume 2: Green Catalytic Systems and Solvents

Edited by Goutam Brahmachari

A fully updated guide to sustainable approaches for synthesizing key heterocycles

Green Synthetic Approaches for Biologically Relevant Heterocycles, Second edition, reviews this significant group of organic compounds within the context of sustainable methods and processes, expanding on the first edition with fully updated coverage and a whole range of additional new chapters on hot topics in the field.

Volume 2 explores green catalytic systems and solvents. Each clearly structured chapter features in-depth coverage of various green protocols for the sustainable use of catalytic processes and solvents. Techniques covered range from metal and magnetic catalysis to organocatalysis and solid acid catalysis, cycloaddition reactions, and varied approaches using ionic liquids.

Fully revised and updated, this book is an essential resource on sustainable approaches for academic researchers, R&D professionals, and students working across medicinal, organic, natural product, and green chemistry.

Key Features

- Provides fully updated coverage of the field with an emphasis on sustainability
- Highlights a range of different eco-friendly solvents and environmentally friendly catalysts
- Collates the experience of a global team of expert contributors

Goutam Brahmachari, PhD, is a professor of organic chemistry at Visva-Bharati University, Santiniketan, India. With more than 22 years of experience in both teaching and research, he has produced over 200 scientific publications including original research papers, review articles, books, and invited book chapters in the field of natural products and green chemistry. He has already authored/edited 25 books from the leading scientific publishers. Prof. Brahmachari serves a number of scientific bodies and received several awards and accolades for his contribution in both teaching and research.

ISBN 978-0-12-820792-5

9 780128 207925

ELSEVIER elsevier.com/books-and-journals