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Azepines, Chemistry, Synthesis and Reactions

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Abstract

Azepines, which consist of a seven-membered cyclic compound featuring six carbon atoms, an additional nitrogen atom, and no double bonds between carbons, form a diverse group within organic chemistry. The fully hydrated form of this compound is called azepam ($C_6H_{13}N$). Compounds and their variants play crucial roles in pharmaceutical research due to their biologic attributes like cancer-fighting, bacteria-killing, fungus-busting, virus-suppressing, and inflammation-reducing capabilities. Various organic molecules found within nature draw attention from scientists across multiple fields due to potential therapeutic applications they offer, such as creating effective medications for various health conditions. Indeed, synthesizing azepines can differ based on the specific condition; however, certain techniques utilize hazardous volatile substances like hydrogen azide for expanding rings into larger ones through conversion processes. Recent research has hinted at utilizing heavier transition metal catalysts including gold, platinum, rhodium, silver, nickel, molybdenum, among others, in an asymmetric approach towards creating these compounds via organic catalysis. Different reactions entail the stepwise formation of azepines through photoinitiated processes. Additionally, this critique delves into elucidating the Specific Antidepressant Response (SAR) associated with azepam compounds. We shall scrutinize numerous methodologies within this assessment and identify notable physiological impacts resulting from those processes.

Keywords: Azepine compounds, ring enlargement techniques, asymmetrical synthetic methods, toxicity of heavy metals, significance in biology

INTRODUCTION

The Azepine Scaffold in Modern Chemical Science

Structural and Electronic Characteristics of Azepines

Azepines represent an essential group of organic molecules consisting solely of six-membered rings containing a lone nitrogen nucleus. The importance of their chemistry lies in an unusual assembly of specific structural elements which sets these compounds apart from typical five-and six-membered ring structures. This feature encompasses intrinsic molecular distortion, typical for moderate-ring structures, along with an electrophilic amine group that substantially enhances its chemical activity (Figure 1) [1]. In the year twenty-twenty-five.

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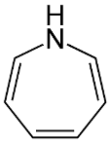

Figure 1. Azepine chemical structure

Essentially, the azepine core usually lacks planarity due to its lack of complete conjugation, making it neither aromatic nor rigidly structured, which allows for considerable molecular movement. The ability of this conformational flexibility isn't confined solely to being an abstract

peculiarity but rather serves as the tangible characteristic responsible for enhancing the scaffolding's applicability in various fields of chemistry. Within pharmaceutical research, this adaptability permits azepines to exhibit numerous structural variations, facilitating their specific interaction with an extensive array of disease-related receptors. However, researchers have harnessed the unique, three-dimensional shape found within specific types of nitrogen-containing compounds called azepines, such as triphenylbenzotriazole (TBA), to minimize harmful molecular interactions known as π-stacking, thereby enhancing their efficiency in optical electronic applications.

Medicinal and Therapeutic Significance

Azepines play an important role within pharmacological research due to their versatile molecular framework, which forms the basis for numerous bioactive substances exhibiting diverse physiological effects. Azepines' integration into pharmaceuticals has led to more than sixty approved drugs, highlighting these compounds' clinical relevance. The azepine derivatives exhibit broad-spectrum pharmaceutical effectiveness across various medical applications. Such actions encompass anti-psychotic effects, mood-stabilizing capabilities, seizure-preventing qualities, as well as cancer-fighting attributes.

Examples of well-known pharmaceuticals derived from fused azepines underscore their significant therapeutic effects: The drug carbamazepine, also known by its brand name Tegretol (Figure 2), is a dibenzodiazepine compound containing a carbamoyl group attached to the nitrogen atom. It serves both as an anti-convulsive medication and an analgesic aid. Historically, it played an important role by being the initial drug used for treating manic episodes in patients suffering from bipolar disorder.

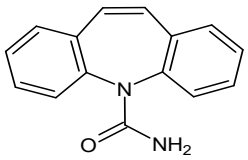

Figure 2. Tegretol.

Synthesis: Dibenazepine underwent reaction with sulfurisocyanatidoyl chloride within methylene chloride under conditions of 30°C (Figure 3).

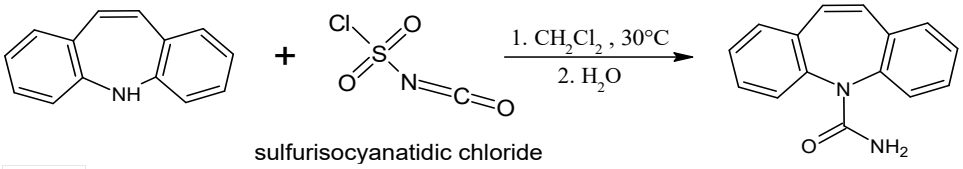

Figure 3. Synthesis of carbamazepine

Quetiapine: A non-traditional psychiatric medication commonly prescribed for treating conditions such as depression, anxiety disorders, seasonal allergies, and urticaria (Figure 4).

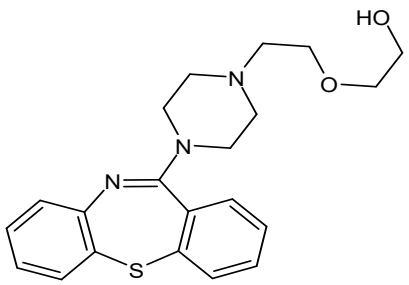

Figure 4. Structure of Quetiapine.

Synthesis: The synthesis involves reacting dibenzo[b,f] [1,4] thiazepine-11(10H)-one with $POCl_3$ before proceeding with an interaction involving 2-[2-(piperidin-4-yl)ethoxy]ethanol according to Figure 5.

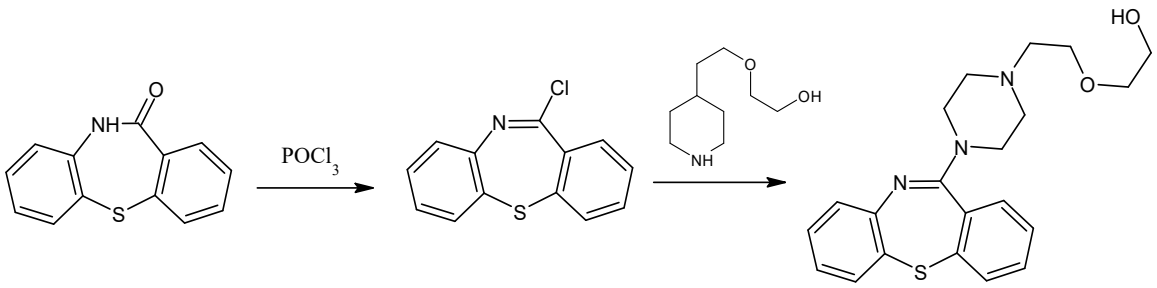

Figure 5. Synthesis of quetiapine

Tianeptine: A unique tetracyclic compound depicted in Figure 6. A medication recognized for reducing anxiety is widely employed in treating severe depression.

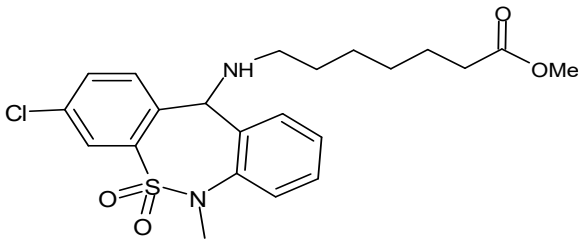

Figure 6. Structure of Tianeptine.

Synthesis: The reaction involves condensing bis-chloro-sulphurated benzodiazepine derivative 3,11-bis-(chloromethyl)-dibenzofuran-6(11H), upon addition of 7-amino-heptyl chloride under acidic conditions catalyzed by triethylamine in an acetone solvent mixture heated between 50°C and 60°C as depicted schematically in Figure 7.

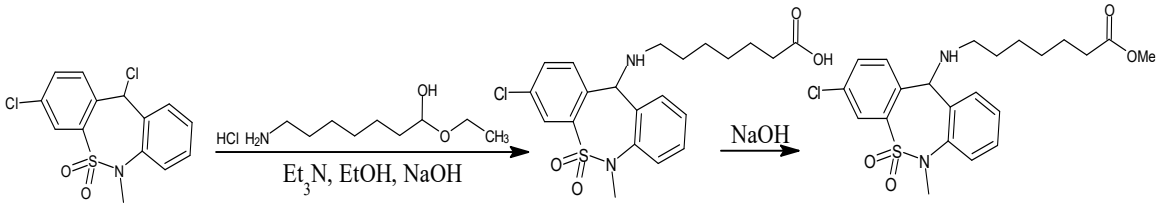

Figure 7. Synthesis of tianeptine.

Azepine's ongoing utility as a therapy guarantees that new, chemically modified synthesis techniques continue to be an important focus within organic and pharmaceutical sciences.

Classical Strategies and the Medium-Ring Synthesis Challenge

Traditional Ring Expansion: Beckmann and Schmidt Rearrangements

Historically, the creation of seven-membered nitrogen-containing compounds has been predominantly achieved through ring-expansion processes involving transformations such as converting cycloketones or their derivatives into lactams (cyclical amides).

Beckmann Rearrangement

In the latter half of the nineteenth century, chemists identified the Beckmann rearrangement as an acidic catalytic method for transforming ketoxime compounds into amide or lactam derivatives. In

order to produce precursor molecules for azepines, it is crucial to undergo the transformation involving cyclic ketoximes like cyclohexanone oxime; this process results in the creation of caprolactam (also known as azepane-2-one) – an organic compound featuring a seven-membered ring structure. Involving the creation of an extremely reactive nitronium cation species as an intermediary step, this compound then transforms into its corresponding amine derivative through hydrolytic processes. (Figure 8). Donaruma and Heldt published their study in 2011.

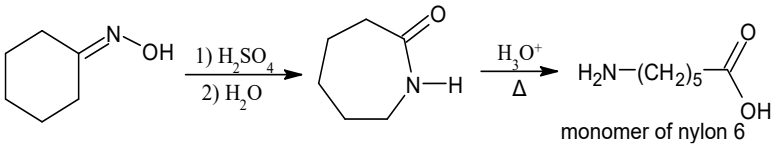

Figure 8. Conversion of six-ring to seven-ring compounds.

Despite historically employing potent yet damaging substances like highly concentrated sulfuric acid or polyphosphoric acid (PPA), contemporary synthetic techniques emphasize environmentally friendly substitutes. Recent research has investigated the application of solid acids, specifically fluorgenium sulfate, for facilitating the transformation of diverse ketoximes into lactams through heating reactions using organic solvents including toluene. Additionally, methane sulfonic acid has been identified as an alternative to highly concentrated mineral acids. The enduring principle remains significant for constructing intricate linked structures like indophenazinyl-fused pyrrolizidine alkaloids derived via the interconversion of their respective oxime forms employing 2,4,6-tribromopyrimidines within dimethylformamide (DMF) [2]. In 2011, Figure 9 was implemented.

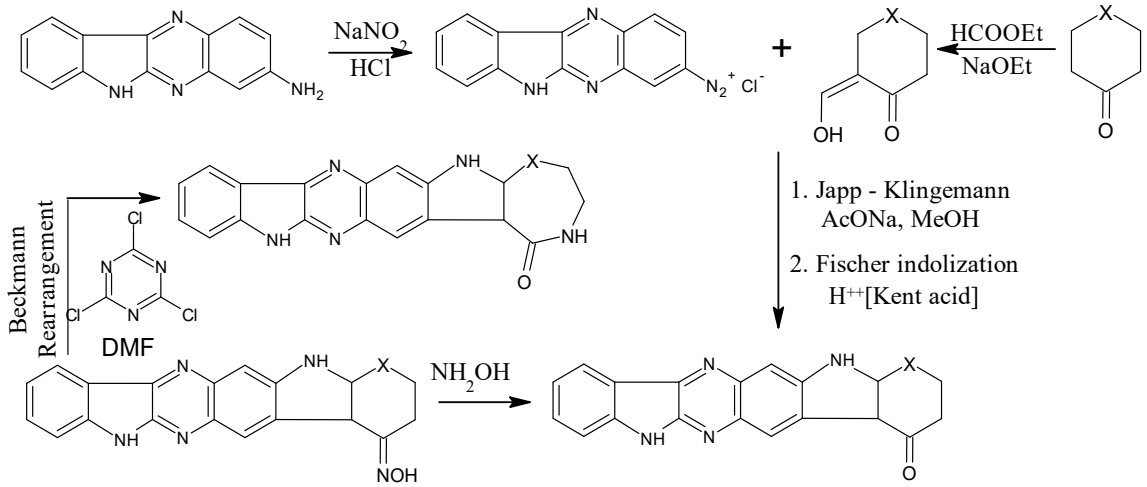

Figure 9. Beckmann rearrangement.

Schmidt Reaction

Another way to expand rings involves breaking a C-C or C-H sigma bond in a molecule and inserting an amine group between two carbonyls like aldehydes or ketones. In cases involving cyclic ketones, the Schmidt reaction usually results in a lactam by converting an azidohydrin intermediate into this ring-expanded amine form via Figure 10 as described in 2022 [3].

A major problem with the classical Schmidt reaction is that it often needs hydrogen azide (H) and other volatile or very toxic azide chemicals. This safety issue limits how widely the reaction can be used. Recently, scientists have been trying to find safer replacements for these dangerous. For example, some Schmidt-type reactions use aryldiazonium salts as the source of nitrogen, along with gold-catalyzed Nazarov cyclization steps. This allows the creation of a wide range of cyclic lactams without needing traditional azide donors.

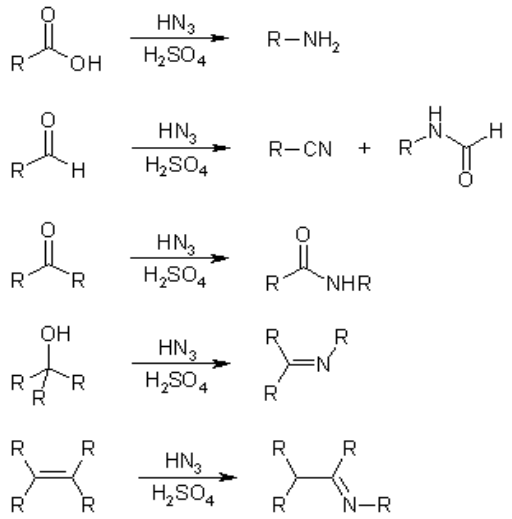

Figure 10. Schmidt expansion method.

The Kinetic Barrier to Seven-Membered Ring Construction

The Challenge of Making Seven-Membered Rings

Even though rearrangement reactions are useful, making medium-sized rings like azepines and azepanes is tricky. There's a natural difficulty in forming seven-membered rings, which makes the cyclization process slow (Figure 11) [4].

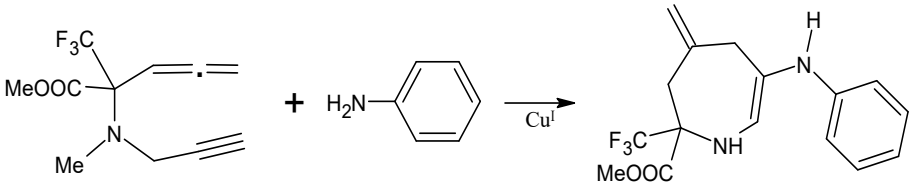

Figure 11. The kinetic barrier causes slow ring formation.

Getting over this slow reaction is a key focus in modern research on azepine synthesis. Most effective methods use highly activated and temporary intermediates or metal catalysts to make the ring-forming step easier. By producing high-energy intermediates the ring-forming step easier. By producing high-energy intermediates like gold-stabilized carbenoids or electrophilic species, the reaction can avoid slow or unfavorable pathways. It's important to keep developing new and better methods for making azepanes and azepines, especially when making compounds with substitution patterns (Figure 12). (Shapiro & Toste, 2008)

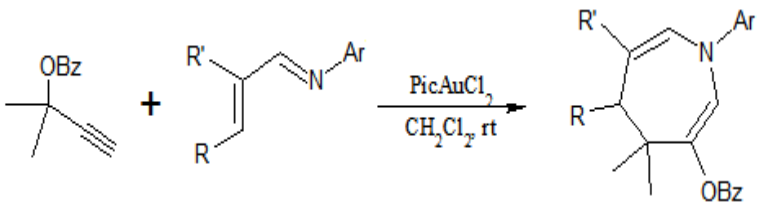

Figure 12. Using transition metals to synthesize azepines.

Modern Synthetic Methods: Efficiency and Selectivity

Today, making azepines relies a lot on catalytic methods that use transition metals or small organic molecules (organocatalysis). These techniques allow for better efficiency, more tolerance for different functional groups, and high stereocontrol, which addresses the issues of older methods.

Transition Metal-Catalyzed Ring Forming Reactions

Catalytic ring-forming reactions with transition metals are powerful and efficient for making complex ring structures, including azepines, by activating substrates in a selective way (Figure 13) [5].

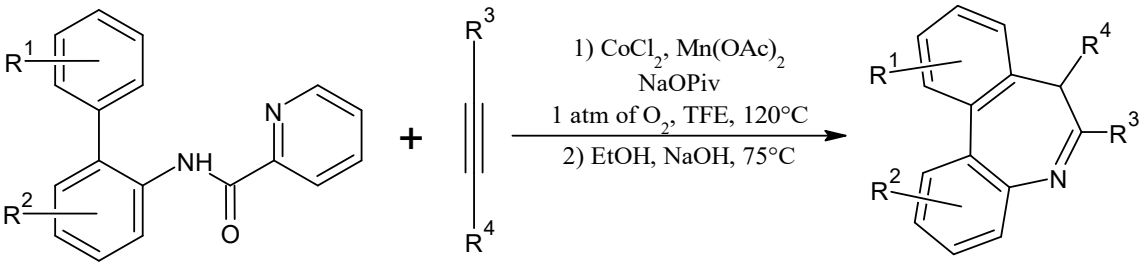

Figure 13. Transition metal-catalyzed ring forming reactions.

Gold-Catalyzed Intermolecular [4+3]-Annulation

A simple and efficient way to make azepines is by using gold (III) to catalyze an intermolecular annulation between propargyl esters and α,β-unsaturated imines. This reaction is technically a [4+3]-cycloaddition and can make both single and fused azepine rings in high yields, often between 55% and 95% (Figure 14) (Shapiro & Toste, 2008)

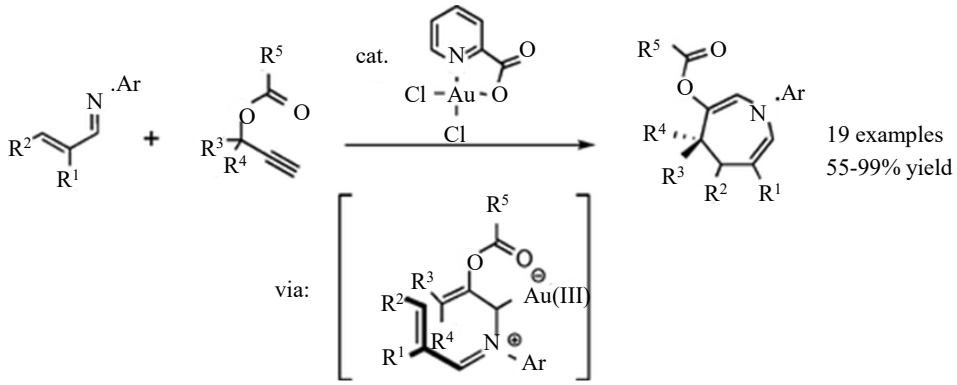

Figure 14. Gold-catalyzed intermolecular Annulation.

This method works through a carefully controlled stepwise mechanism, rather than a single step.

The process starts with the gold promoting isomerization of the propargyl ester, forming a gold-carbenoid intermediate (A). This highly reactive species then reacts with the nucleophilic imine nitrogen to form an allylgold intermediate (B). The seven-membered ring is formed by the intramolecular nucleophilic attack of the allylgold part onto the iminium electrophile, which is guided by is guided by a specific transition state. The gold catalyst helps the reaction avoid the normally slow seven-membered ring closure process. This reaction works with a wide range of imine propargyl ester structures. The highest yields are usually when the imine has electron-rich N-aryl groups. The reaction can handle different aryl and aliphatic groups attached to the double bond. Also, it works well with useful functional groups like vinyl bromides, leading to bromoazepines that can be used in further reactions like cross-coupling.

Copper-Catalyzed Tandem Amination/Cyclization

Another effective method involves using Cu(I) to catalyze a tandem amination and cyclization of functionalized allenynes with primary or secondary amines.

This method is especially good for making trifluoromethyl-substituted azepin-2-carboxylates and their phosphorus counterparts. This approach is important for making azepine and azepane compounds

that are useful in drug discovery. Adding fluorinated groups, like the trifluoromethyl group, helps meet the needs of the pharmaceutical and agrochemical industries. Fluorine can improve a drug's lipophilicity, stability, and properties like the pKa, which are important for drug performance. By combining ring formation and group introduction in a single, efficient process, this Cu(I) method provides a strong way to make challenging fluorinated azacycles (Figure 15) [6].

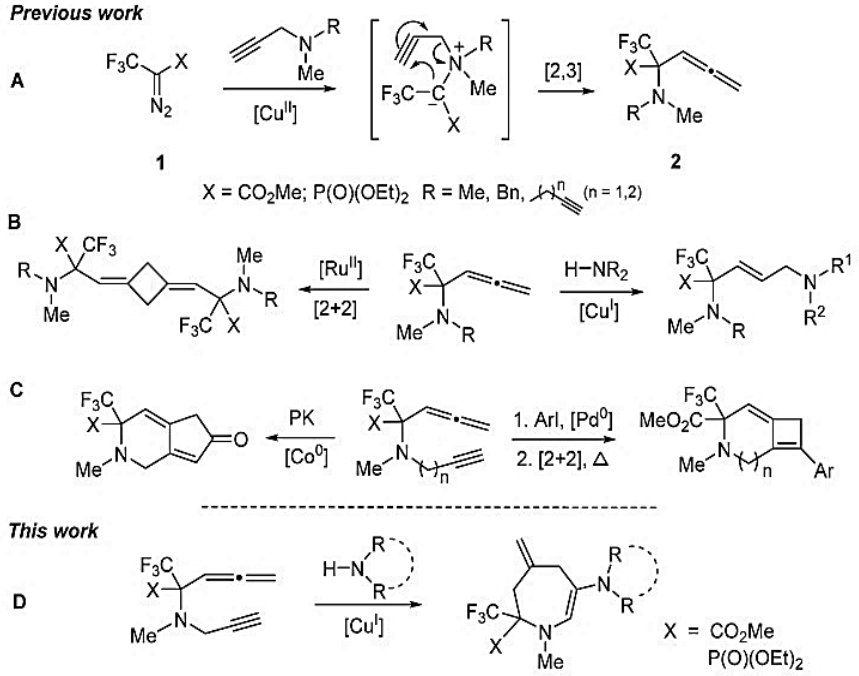

Figure 15. Copper-catalyzed tandem amination/cyclization.

Asymmetric Synthesis: Making Pure Enantiomers

It's very important to make azepines in a way that gives pure enantiomers in medicinal chemistry, as the shape of a drug can affect its effectiveness and safety (Figure 16) [7].

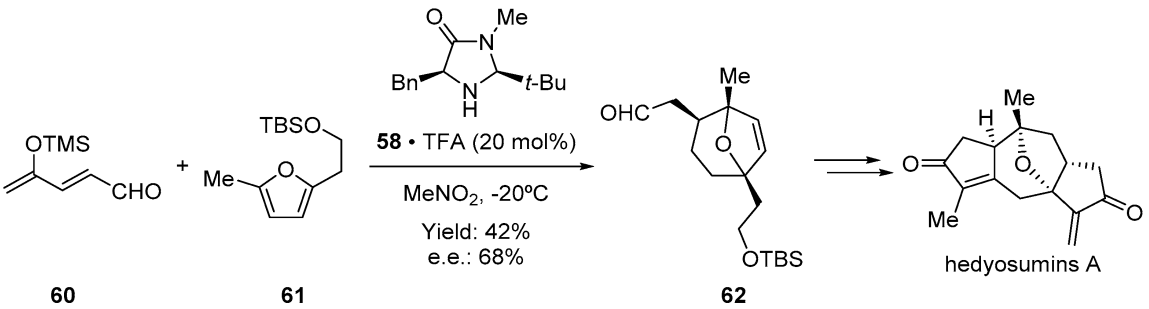

Figure 16. Asymmetric synthesis of azepine.

Asymmetric Organocatalytic Routes

Asymmetric organocatalysis uses small, chiral organic molecules to speed up reactions, offering a clean and metal-free way to make enantiomerically pure azepine derivatives. One good example is using chiral Brønsted acid catalysts in an asymmetric aza-Piancatelli rearrangement/ Michael addition. This two-step process works under easy conditions and makes bridged tetra hydrobenzo [b] azepine and oxepine structures with high control over enantiomers (ee) and diastereomers(dr). Using organocatalysis fits with green chemistry by avoiding expensive or harmful metal catalysts in the final product (Figure 17) [8].

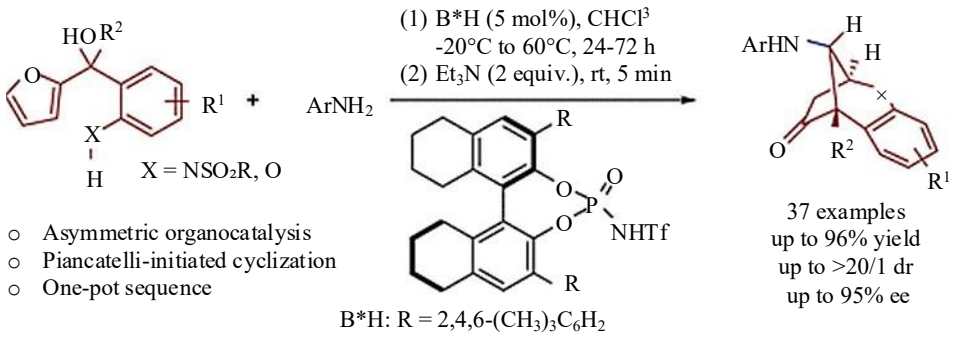

Figure 17. Asymmetric organocatalytic synthesis of azepine.

Metal-Catalyzed Asymmetric Hydrogenation

For existing azepine-based drug structures, enantioselective hydrogenation is important based drug structures, enantioselective hydrogenation is important. An efficient and highly selective IR-catalyzed hydrogenation has been developed for seven-membered cyclic imines made from benzodiazepinones and benzodiazepines. This process gives direct access to chiral amines that are common in many drugs and natural products. For example, the enantioselective synthesis of Aptazepine, a strong tetracyclic antidepressant, uses an asymmetric transfer hydrogenation step, achieving very high enantiomeric purity (up to 98% ee) after crystallization (Figure 18) [9].

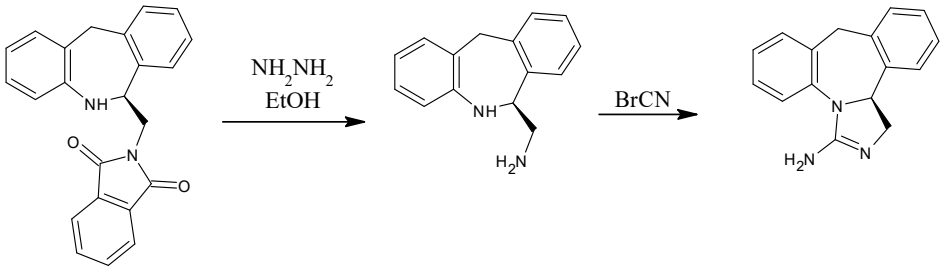

Figure 18. Asymmetric hydrogenation.

The success of these metal-catalyzed asymmetric reactions depends on the design of the stabilizing ligands. Phosphorus and nitrogen-containing (PN) chelating ligands are among the best used in homogeneous asymmetric catalysis. These ligands often use features like axial chirality (atropisomerism) to ensure precise control over the stereochemistry during the chemical reaction. The P,N ligands help maintain specific shapes around metals like iridium or rhodium, which determine how the intermediate steps behave and lead to a product with high stereochemical purity, like azepine.

Table 1 shows how different methods used today for creating azepines compare in terms of their features and what they aim to make.

Table 1. Comparison of advanced catalytic methods for azepine synthesis

Methodology	Key Substrates	Primary Advantage/Selectivity	Target Structure
Gold(III)-Catalyzed [4+3] Annulation	Propargyl esters, alpha,beta-unsaturated imines	Intermolecular, High Functional Group Tolerance, Efficiency	Monocyclic and Fused Azepines
Cu(I)-Catalyzed Tandem Cyclization	Functionalized allenynes, Primary/Secondary Amines	Selective Trifluoro methylation, Functionalized Azepanes/Azepines	Azepin-2-carboxylates (e.g., fluorinated cyclic amino acids)
Chiral Brønsted Acid Organocatalysis	Appropriate precursor imines/enamines	High Enantio- and Diastereoselectivity, Metal-Free	(a) Bridged Tetrahydrobenzo [b] azepine derivatives
Photocatalytic Dechlorinative Cyclization	Dichloro-azepinedione precursors, Anilines	Late-Stage Construction, Mild Conditions	Indoloazepinediones, Fused Heterocycles

Photocatalysis is an expanding area with unique benefits for making complex heterocyclic compounds, mainly because it can create very reactive molecules under mild conditions.

Using Multiple Photoinduced Reactions

Photocatalysis has been used to make fused azepine systems, which are hard to build. For instance, the indoloazepinedione core, a complex ring structure, can be made in two steps by using two photoinduced reactions. The first step involves an intramolecular (5+2) photocyclo- addition of an alkene-tethered maleimide, forming a dichloro-azepinedione. The second step is a photocatalytic dechlorinative cyclization onto an aromatic ring (added earlier through amination), finalizing the indole ring structure (Figure 19) [10].

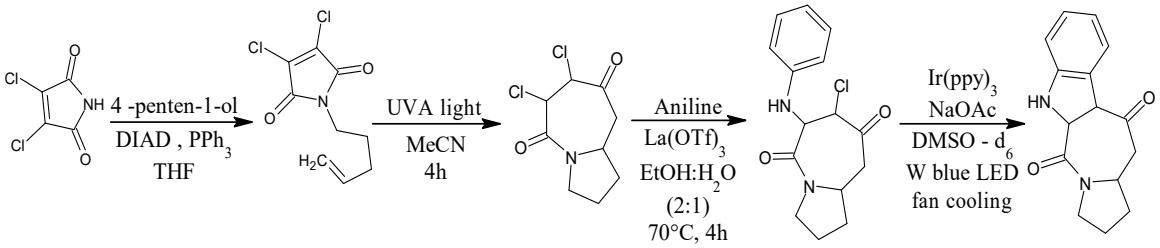

Figure 19. Sequential photoinduced reaction.

This method of building late is very useful. It allows chemists to make the indole ring several steps before the final light-driven reaction, giving more freedom to modify the precursor molecules (like the benzenoid part of the indole) before completing the molecule. This flexibility is important for tweaking the molecule's properties for specific uses.

Azepines as Photocatalysts

Azepine derivatives are not only made but also serve as functional elementsin catalysis and materials science. Tribenzo [b,d,f] azepine (TBA) derivatives have been explored as part of photocatalysts (PCs). These azepines can act as electron donors with good light properties and suitable redox potential. The antiaromatic nature of the TBA core leads to unique features, such as a twisted structure and better reverse intersystem crossing (RISC), making them a good alternative to traditional nitrogen donors in photocatalytic systems. Incorporating azepines into photocatalysis shows how the same structure can be used both for making new materials and for further chemical changes (Figure 20) [11].

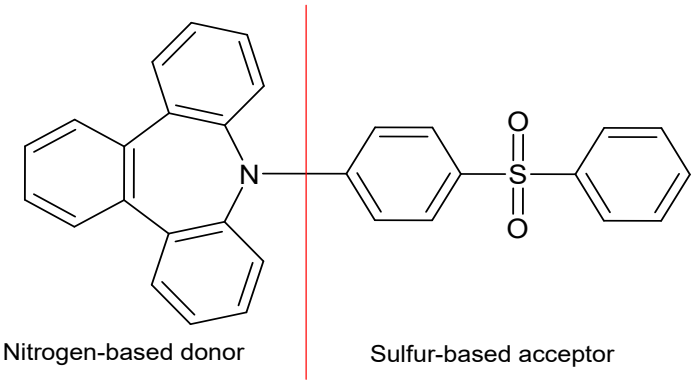

Figure 20. Tribenzo [*b,d,f*] azepines as donor in D-A photocatalysts.

Applications: Structure-Activity/Property Relationships (SAR/SPR)

The real value of azepine chemistry comes from linking the structure of these compounds to their biological or material properties. This includes studying how changes in structure influence function in both drug design (Structure-Activity Relationships, SAR) and in materials (Structure-Property Relationships, SPR).

Medicinal Chemistry: SAR of Tricyclic Azepine Antidepressants

Tricyclic systems, such as the dibenzoazepine and dibenzodiazepine scaffolds, are important parts of many medicines that affect the central nervous system (CNS). Looking at how chemical changes affect biological function helps in designing new drugs (Figure 21) [12-14].

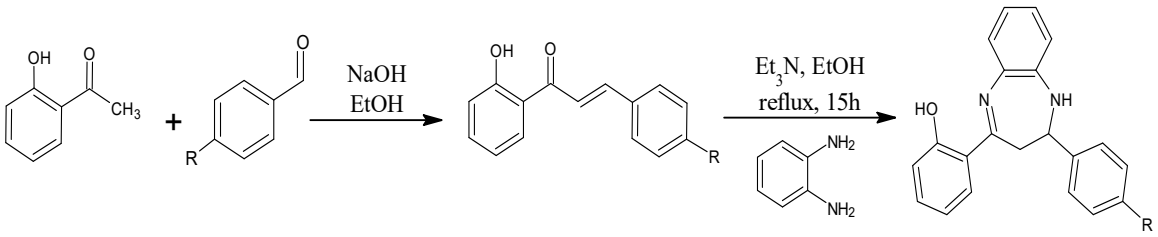

Figure 21. SAR of azepines as antidepressant.

Impact of Substituents

Studies show that the electronic nature of groups on the aromatic parts of azepines greatly affects affects their pharmacological effects. A main rule is that electron-withdrawing groups (EWGs), such as fluorine or chlorine, often maken the compounds more active, including antidepressant and anxiolytic effects. In contrast, adding electron-donating groups (EDGs), like methyl or methoxy, generally leads to less activity. This pattern suggests that EWGs help in making the molecule's charge distribution better for binding to its target sites (like specific GABAergic or monoamine targets). This optimization might improve interactions by making the molecule fit better into the receptor or change its lipophilicity and pKa, which are important for how well it crosses cell membranes and binds to receptors. The preference for EWGs supports methods like Cu I catalyzed trifluoromethylation, which can add these groups specifically.

Table 2 shows examples of azepine-containing drugs and their uses, highlighting how this core structure can lead to many different applications.

Table 2. Representative azepine-containing drugs and pharmacological activity

Drug Class/Scaffold	Key compound example	Primary therapeutic class	Structural Role/Core
Dibenzoazepine	Carbamazepine (Tegretol)	Anticonvulsant, Analgesic	Tricyclic core, key anticonvulsant scaffold
Dibenzodiazepine	Quetiapine	Atypical Antipsychotic	Seven-membered N-heterocycle for flexibility
Pyrrolobenzodiazepine	Aptazepine	Antidepressant	Fused polycyclic scaffold, highly chiral target
Azepane Derivatives	Trifluoromethyl-Azepanes	Anticancer, Antidiabetic, Antiviral	Saturated, conformationally flexible ring system

Materials Science: Azepines in Optoelectronics (TADF Emitters)

Beyond drug development, azepines are also important in materials science, especially in the creation of high-performance Thermally Activated Delayed Fluorescence (TADF) emitter for Organic Light-Emitting Diodes (OLEDs).

The Role of Non-Planar Conformation

The structure of azepines is used to achieve the best photophysical properties. In TADF materials, high efficiency is obtained by using the efficient reversal of intersystem crossing (RISC) to repeat triplet excitons. Making sure that non-radiative decay paths (like quenching due to molecule stacking) are minimized is key to a good quantum efficiency.

Table 3 collects the critical structure-activity/property relationships (SAR/SPR) that guides important research directions.

Table 3. Critical structural requirements for azepine functionality (SPR Summary)

Application Field	Key Structural Requirement	Reasoning/Function	Implied Synthetic Focus
Medicinal Chemistry (SAR)	Electron-Withdrawing Groups (EWG) on Ar-rings	Enhances biological activity through optimized electronic profile/binding.	Selective fluorination/nitration methods (e.g., Cu I) catalysis).[11]
Materials Science (TADF)	Non-planar, Twisted Azepine Core (e.g., TBA)	Minimizes π-π stacking; promotes high reverse intersystem crossing (RISC) for high EQE.[2]	Modular, late-stage synthesis of polycyclic, spatially demanding cores.

CONCLUSION

Azepine derivatives like tribenzo [b,d,f] azepine (TBA), are used as strong electron donors in donor-acceptor TADF systems. The twisted, non-polar structure of the azepine ring helps in this application. This structure stops close packing of molecules (π-π aggregation), which usually causes loss of light in solid state. This leads to better light emission and less energy loss, allowing azepine-based emitters to reach very high efficiency with external quantum efficiency (EQE) values over 40% in some devices. This dual use—building a complex structure and also giving the necessary shape for functioning—shows the versatility of azepine in chemistry.

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