



Advances in Organic Synthesis

Editor:
Atta-ur-Rahman, *FRS*

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PREFACE

This volume of *Advances in Organic Synthesis* presents recent exciting developments in synthetic organic chemistry. It covers a range of topics including important researches on novel approaches to the construction of complex organic compounds. The chapters are written by authorities in the field. Topics covered in this volume include updates in asymmetric synthesis of natural compounds, ynamide chemistry and its application in organic synthesis, heterocyclic chemistry, application of tin(II) salts in specific organic reactions and the use of (E)-N-methyl-1-(methylthio)-2-nitroethenamine (NMSM) as an ambiphilic synthon in organic synthesis.

This book should prove to be a valuable resource source for organic chemists, pharmaceutical scientists and postgraduate students seeking updated and critically important information on recent important developments in synthetic organic chemistry. I hope that the readers will find these reviews valuable and thought-provoking so that they may trigger further research in the quest for new developments in the field.

I am thankful to the efficient team of Bentham Science Publishers for the timely efforts made by the editorial personnel, especially Mr. Mahmood Alam (Director Publications), Mr. Obaid Sadiq (in-charge Books Department) and Ms. Asma Ahmed (Manager Publications).

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CHAPTER 1

Remarkable Advances in the Asymmetric Synthesis of Biologically Active Natural Compounds from the Advent of Chiral Auxiliaries

Gaspar Diaz-Muñoz^{1,*}, Izabel Luzia Miranda¹, Suélen Karine Sartori¹, Daniele Cristina de Rezende¹, Jefferson Viktor Barros de Paula Baeta², Fernanda Rodrigues Nascimento² and Marisa Alves Nogueira Diaz²

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Abstract: This chapter reports advances in synthetic methodologies employing chiral auxiliaries for the stereoselective synthesis of biologically active natural molecules. Derivatives of naturally occurring compounds such as amino acids, carbohydrates, and terpenes, chiral auxiliaries have been described as an essential aid for the construction of highly complex molecules. Among these auxiliaries, we highlight those of Evans, Corey, Yamada, Enders, Oppolzer, Kunz, Meyers, and Schöllkopf, whose contributions led to a remarkable progress in asymmetric synthesis in the last decades and continue to bring advances until the present day.

Keywords: Asymmetric Synthesis, Biologically Active Compounds, Chiral Auxiliaries, Corey's Chiral Auxiliary, Evans' Oxazolidinones, Enders, Kunz, Meyers, Oppolzer, Schöllkopf, Yamada.

INTRODUCTION

In the last decades, chiral auxiliaries have been widely used in the synthesis of enantiomerically pure compounds [1].

The growing interest of the scientific community in the asymmetric synthesis of biologically active compounds occurred from the discovery of substances of natural origin, which often have only one of the enantiomers with pronounced pharmacological activities only in their enantiomerically pure form [2, 3].

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A historical and striking incident that served as a lesson for global public health, known as the thalidomide tragedy, occurred in the 1960s when the racemic mixture of thalidomide began to be used to relieve nausea in pregnant women, leading to a large increase in the incidence of fetal malformations. This was later associated with the teratogenic activity of thalidomide's *S*-enantiomer, which did not exhibit the desired pharmacological activities exhibited only by the *R*-enantiomer [4, 5].

This regrettable event was a general call for pharmaceutical industries to adopt new policies, employ a more stringent care in the production of new medicines, and market drugs in their enantiomerically pure forms, when necessary.

Commonly, enantio- or diastereomerically pure compounds can be produced employing a step of chemical resolution, such as chemical or enzymatic desymmetrization, enzymatic kinetic resolution or racemic modification, or also by means of a synthetic route having as starting material a substrate, reagent, solvent or enantiomerically pure catalyst, characterizing an asymmetric synthesis [2].

Several methodologies aimed at inducing stereoselectivity in chemical reactions have been developed. In this context, the use of chiral auxiliaries is a powerful and successful tool widely used to obtain intermediates and final products of total synthesis [2].

Chiral auxiliaries are molecules capable of temporarily binding to the starting compound, thus inducing chirality in one or more steps of a synthetic route [3].

Most of the available chiral auxiliaries are derived from compounds of natural origin: amino acids, carbohydrates, terpenes, among others [3].

Some factors influence the choice of the appropriate chiral auxiliary for each reaction and must also be taken into account for the development of new auxiliaries. A good chiral auxiliary must have certain characteristics to be employed in asymmetric synthesis reactions: the addition and removal steps of the auxiliary should be performed easily or under mild conditions and must generate a high chemical yield, the chiral transfer step should occur with high diastereoselectivity, and the auxiliaries should lead to the desired products with excellent enantioselectivity. As they are often costly or non-trivial and used in stoichiometric quantities, it is of great interest that these auxiliaries be reused or recycled [3] at the end of the synthetic route.

Currently, there is a wide range of efficient chiral auxiliaries frequently used in carbon-carbon bond formation reactions with high stereoselectivity and in the

synthesis of compounds of natural origin and compounds with pronounced pharmacological activity. Some examples of common chiral auxiliaries are shown in Fig. (1).

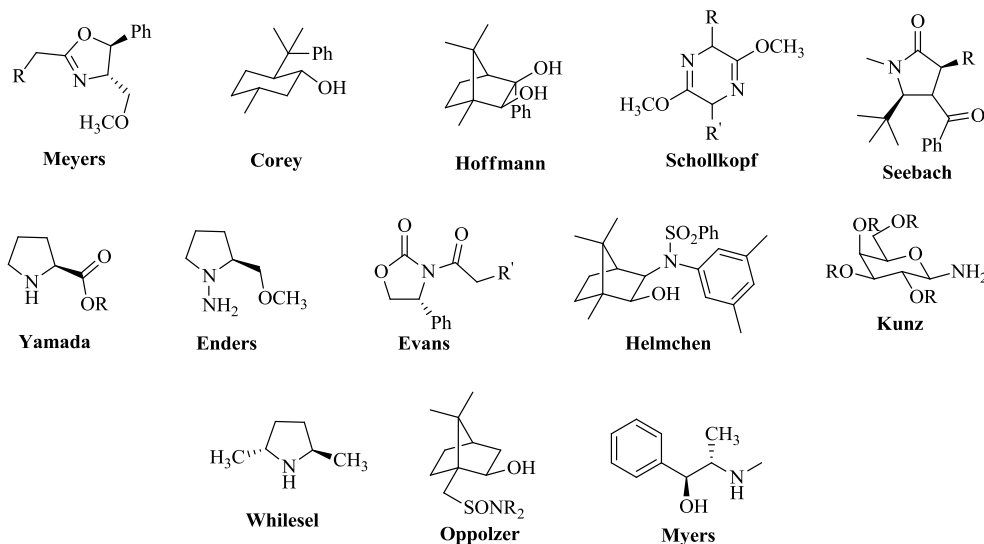


Fig. (1). Selected chiral auxiliaries that have been successfully employed in asymmetric synthesis.

Corey's chiral auxiliary, named (+)-8-phenylmenthol, and its enantiomer have been classified among the most versatile chiral auxiliaries of asymmetric organic synthesis and have an important historical value, since they were the first of their kind to be added to the arsenal of chiral auxiliaries known today [6].

Evans' oxazolidinones are auxiliaries that also deserve to be highlighted [1, 7, 8]. The increasing interest in this class of auxiliaries may be evidenced by the structural variations of this genus (Fig. 2) following the report of the first oxazolidinone by Evans [1].

Next, some of the main chiral auxiliaries will be addressed individually, with their most relevant contributions to the field of asymmetric synthesis, according to our point of view, indicated through examples.

EVANS' OXAZOLIDINONES

Evans' chiral auxiliaries represent one of the most widely used auxiliaries in asymmetric total synthesis [3]. The most prominent application of oxazolidinones undoubtedly occur in the reactions of α -alkylation, *syn*-aldol, 1,4-addition, and intramolecular Diels-Alder cycloaddition reactions [3, 9].

The Chemistry of Ynamide and Its Application in Organic Synthesis

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Abstract: Ynamide, is an understudied but attractive class of alkynes, activated by the donating ability of the nitrogen adjacent to alkynes. With the nucleophilicity on β -carbon and the electrophilicity on α -carbon of ynamides, this review summarizes the syntheses of ynamides and miscellaneous reactions - oxidation, rearrangement, cyclization, and cycloaddition to construct complicated heterocyclic rings. The synthetic methodologies were further applied into natural products synthesis, *e.g.* marinoquinolines A and C, aplidiopsamine A, rigidin A, and 7-azaserotonin derivative.

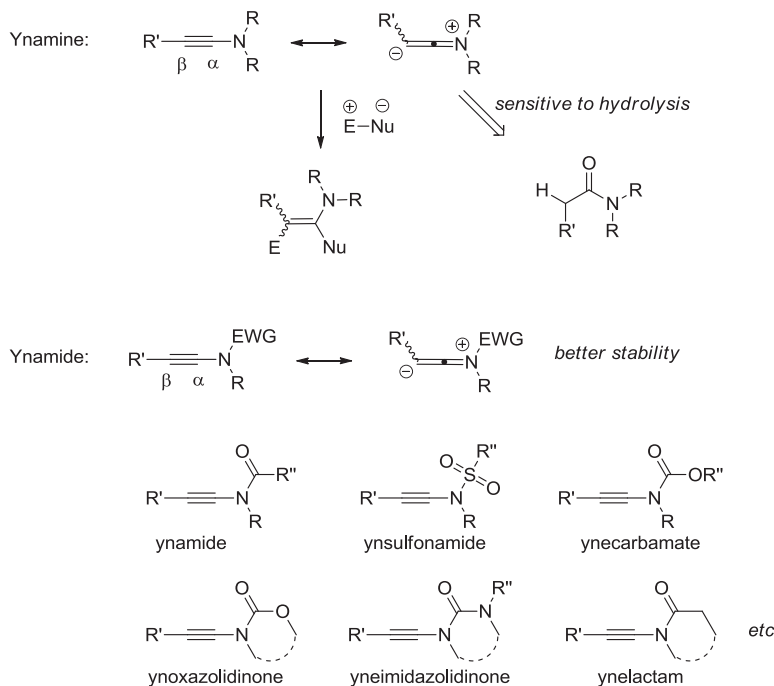
Keywords: Dipolar Cycloaddition, Haloenamide, Keteniminium, Polycyclic Alkaloids, Thioenamide, Ullmann Coupling, Witulski Rearrangement, α -Ketoimide, Ynamide, Yndiamide.

INTRODUCTION

The carbon-carbon triple bond is one of the most fundamental and valuable functional groups in the organic synthesis. A heteroatom substitution on the triple bond further enriches the reaction versatility. One useful substrate is ynamine, which contains a nitrogen atom directly connected to the triple bond. Conjugation of the nitrogen lone pair readily assists the electrophilic functionalization of the β -position of ynamines, and α -carbocation initiated nucleophilic addition or cyclization reactions (Scheme 1). However, the synthetic utility of ynamines remained limited due to difficult preparation and handling. They are liable to hydrolyse to amides in an expensive manner. The ynamides were therefore tunable by introducing diversified amides, *i.e.*, amides, sulfonamides, carbamates,

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oxazolidinones, imidazolidinones, and lactams (Scheme 1). Ynamides, with weakened electron-donating electron lone pair of the nitrogens towards the alkynyl motifs, have been found to be more stable and practicable than conventional ynamines.



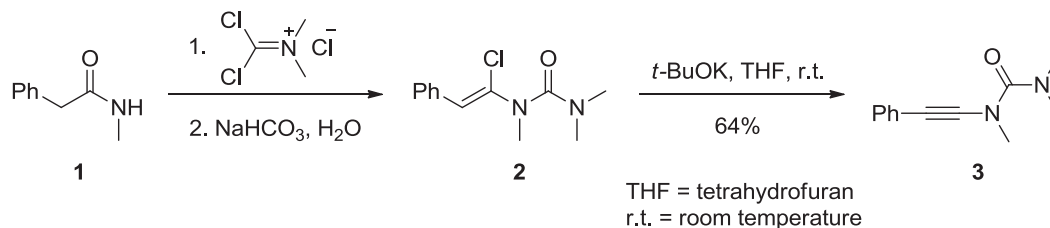
Scheme 1. General structures of ynamine and ynamide.

The ynamide chemistry, emerged several decades ago, has been gaining more and more attention since 2000. Hsung's group [1, 2] and Evano's group [3, 4] have published elegant reviews to cover the development. This review focuses on recent developments of syntheses and applications of ynamides after 2010, in order to reveal the value of ynamide chemistry in organic synthesis.

PREPARATIONS OF YNAMIDES

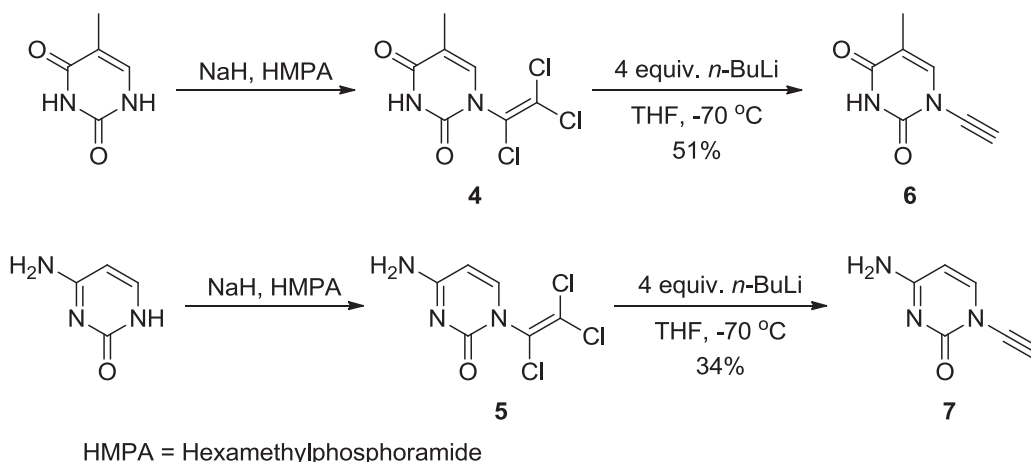
Dehydrohalogenation

Dehydrohalogenation of halo-substituted enamides was the initial method of preparing ynamides. Viehe *et al.* [5] reported the first case of preparing ynamides. *N*-(1-chloroalkenyl)urea **2**, generated from secondary acetamide **1** and phosgene immonium chloride, underwent dehydrochlorination at room temperature with *t*-BuOK to afford *N*-alkynylurea **3** in moderate yield (Scheme 2).



Scheme 2. The first case of synthesizing ynamide.

Another case is thymine/cytosine [6] derived chloroenamides **4** and **5**, obtained by nucleophilic additions of thumines/cytosines to tetrachloroethylene. Dechlorination (lithium-chlorine exchange) of **4** and **5** with *n*-BuLi occurred smoothly at $-70\text{ }^{\circ}\text{C}$ to render ynamides **6** and **7** in 51% and 34% yields, respectively (Scheme 3).



Scheme 3. Lithium-chlorine exchange of chloroenamides to ynamides.

Hsung and co-authors [7] further explored the substrate scope to β -bromoamides, prepared by bromination of the corresponding enamides **8**. E_2 elimination of hydrobromide from β -bromoamides **9** with *t*-BuOK afforded ynamides **10** in 36~88% yields (Scheme 4), under these conditions, pyrrolidinones, oxazolidinones and imidazolidinones were tolerated. However, transformation of *E*-isomers of **9** into ynamides failed.

Brückner [8, 9] modified the substrates for ynamides *via* dehydrohalogenation. β,β -Dichloroenamides **12**, obtained by Corey-Fuchs reaction of *N*-formyl-tosylamides **11**, which were converted to terminal ynamides **13** in satisfying yields, according to lithium-halogen exchange (Scheme 5). β,β -Dibromoamides

Carbon-Heteroatom Bond Formation for Medium Ring Heterocycles

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Abstract: In major classes of natural products and pharmaceutical compounds, functional groups containing carbon-heteroatom bonds are present and often responsible for significant biological activities. Among them, medium-ring heterocycles are found in a wide range of drug candidates. While the synthesis of five- and six-membered ring systems is quite common, however, the formation of seven-, eight- and nine-membered heterocycles is not as abundant as entropy factors and transannular interactions often hinder the cyclization method. The ubiquitous presence and use of heteroatoms in both synthetic and naturally occurring pharmaceutical compounds support the review of carbon-heteroatom (particularly, C–N, C–O, C–S, C–S, C–Se, C–Te) bond-forming reactions reported in the literature. In general, the nucleophilic cyclization, organocatalyzed reactions, green synthesis, heterocycloaddition, ring-closing metathesis, radical cyclization, metal-mediated transition cycloaddition, macrolactonization are discussed as the most commonly used strategies for medium-ring construction. The ring expansion strategies, such as pericyclic and sigmatropic rearrangements, play an important role in the formation of C–X bonds. The challenges faced involving structural complexity and biological activities prompted us to review the literature for the synthesis of the heterocycles of the medium-ring size. This chapter is dedicated to recent developments for the construction of C–X bonds in seven-, eight- and nine-membered heterocycles.

Keywords: Green synthesis, Heterocycles, Medium ring, Metal catalysed cyclization, Nucleophilic cyclization.

INTRODUCTION

Heterocycles have attracted much attention of chemists owing to their interesting architecture and profound bioactivities. These represent a privileged class of compounds of natural origin essential to life, such as nucleic acids, naturally

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occurring pigments, vitamins, hormones and antibiotics, and most hallucinogens. Their unique ability to be used as biomimetics as well as active pharmaco-core has rendered them valuable motifs in the arena of pharmaceuticals as low molecular weight lead compounds in drug design. Over the decades, these compounds have set a benchmark in pharmaceutical research, with many of them being active drugs to date or have acted as templates for different drug molecules [1]. In addition, heterocycles have also become a part of the modern society as lead compounds for pesticides, herbicides, fungicides, dyes, plastics, and other application-oriented products. Functional groups containing C–hetero bonds are found in major classes of natural and non-natural pharmaceutically active molecules constituting nearly 90% of the active pharmaceuticals. Among these, medium rings heterocycles represent an important motif for a wide range of drug candidates. In particular are the seven-membered azepine, oxepine, thiazepine, or the eight-membered ones oxocin, azocine, and other associated heterocyclic analogs have created a stir among the biological community, being moieties associated with significant biological relevance. Few representative molecules (E)- pterulone (**1**) [2], bauthinoxepin J (**2**) [3], buflavine (**3**) [4], helianuol A (**4**) [5], paecilquinone E (**5**) [6], sclerotigenin (**6**) [7], circumdatin F (**7**) [8], cleavamine (**8**) [9], balasubramide (**9**) [10], galanthamine (**10**) [11], cladoacetal A (**11**) [12], balanol (**12**) [13], imipramine (**13**) [14], diazepam (**14**) [15] and loxapine (**15**) [16] are shown in Fig. (1). For example, the seven-membered heterocycle imipramine (trade name Prazepine) is the first of the tricyclic antidepressants, and the tranquillizer diazepam (trade name Valium) is one of the oldest medications used till date.

STRUCTURAL EFFECTS

As introduced by Prelog and Brown the term “medium-sized ring” is usually referred to cyclic compounds having eight to eleven members; however, seven- and twelve-membered rings are frequently included for comparison purposes, particularly when analyzing the conformational effects within these systems [17a,b].

As the size of the ring increases, the range of compounds that can be obtained by varying the number, type, and location of the heteroatoms increases enormously.

Nevertheless, the chemistry of heterocyclic compounds with rings seven-membered or larger is much less developed than that of five- and six-membered ring heterocycles, although these compounds are usually stable with immense practical applications. The synthetic community is always on the run for developing newer methodologies for the construction of 7, 8 and 9 membered heterocycles since decades [18]. Although, five- and six-membered ring systems

are quite common but the formation of seven-, eight- and nine membered ring heterocycles have encountered several difficulties as cyclization strategies are often hampered owing to entropy factors and transannular interactions [19].

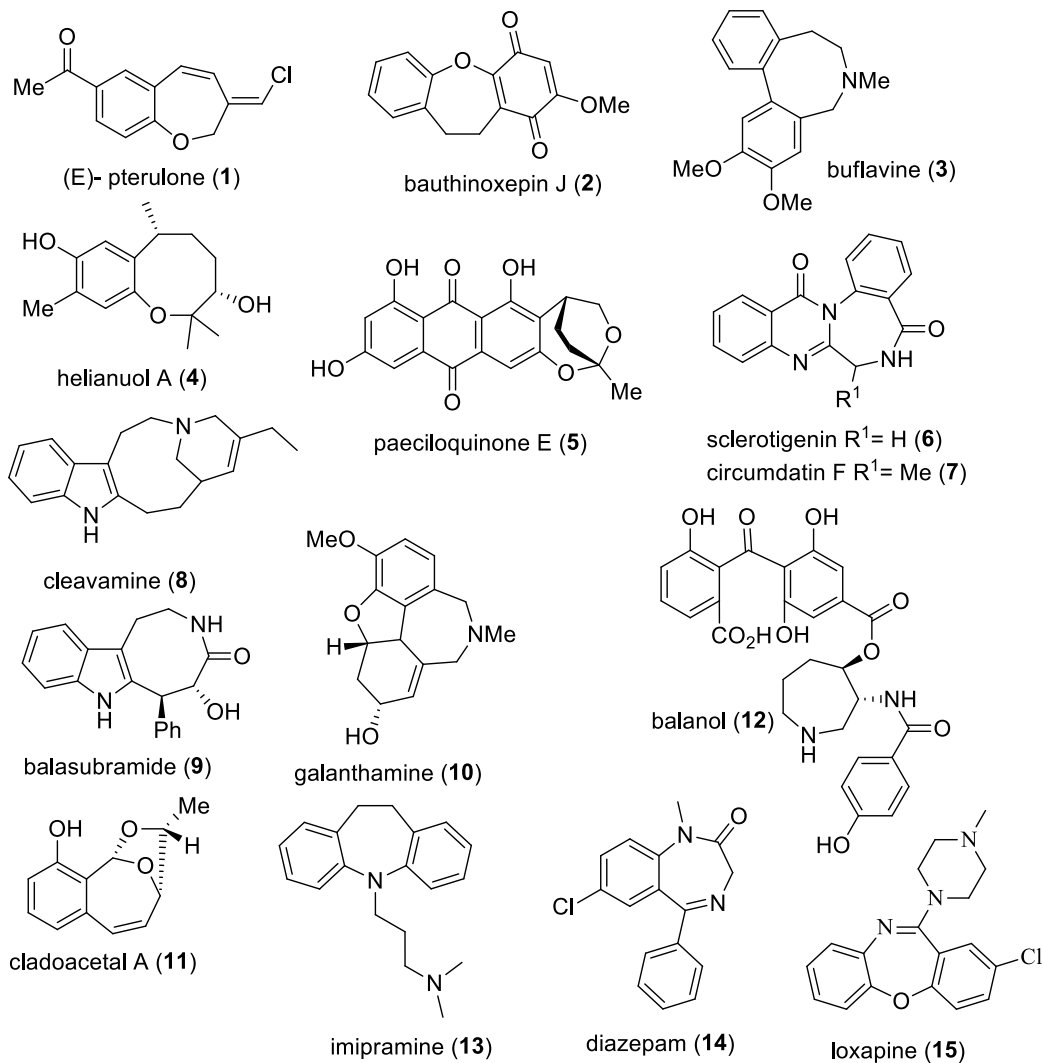


Fig. (1). Some pharmaceutically important medium ring heterocycles.

RINGS WITH HETEROATOMS OTHER THAN O, N, AND S

The word heterocycle actually indicates the presence of at least one heteroatom within the ring. Though the commonest among the rings are five- or six-members containing mainly nitrogen (N), oxygen (O), or sulfur (S) atom(s), in addition, a

Tin(II) Salts: A Versatile and Efficient Lewis Acid Catalyst in Reactions to Add Value to the Glycerol and Terpenic Alcohols

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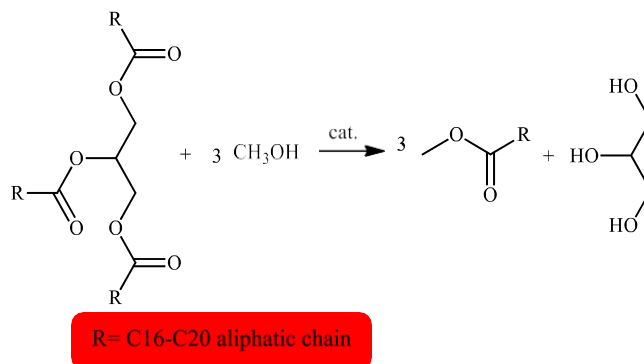
Abstract: Glycerol is a renewable origin compound that has been generated on a large scale in biodiesel production processes. Terpenic alcohols are abundant raw material present in several essential oils. Therefore, developing processes to convert this cheap feedstock to a more value-added compound is important from an economic and environmental viewpoint. This work summarizes the main advances obtained in different kinds of tin (II) salts-catalyzed reactions in the last decade, where the goal substrates were glycerol and terpenic alcohols. Tin (II) halides are water-tolerant Lewis acids, solid, inexpensive and easy handling, which showed be efficient catalysts in reactions of carbamoylation and ketalization of glycerol, as well as in esterification of terpenic alcohols. The products generated from terpenic alcohol esterification are valuable ingredients for fragrance, agrochemicals and pharmaceutical industries. Conversely, esters and glycerol ketals are useful as fuel additives. Terpenic carbamates are ingredients in agrochemical synthesis. Therefore, due to great success on these reactions, Sn (II) catalysts are an attractive option to the traditional Bronsted acid catalysts.

Keywords: Esterification, Glycerol, Ketalization, Terpenic Alcohols, Tin(II) Catalysts.

INTRODUCTION

As the petroleum reserves have progressively diminished, a growing increase in search by alternative sources of renewable fuels has been noticed in the wide world. The biodiesel is a liquid fuel that can be blended to the diesel and has attracted the interest due to low environmental impact. Typically, the production of biodiesel is performed through transesterification of animal fats or vegetable oils with methyl or ethyl alcohol, leading to a formation of monoalkyl ester with similar properties to the fossil diesel (Scheme 1).

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Scheme 1. Methanolysis of triglycerides.

Currently, the widespread use of biodiesel has two disadvantages:

1. The impact triggered by the price of vegetable oil on the final cost of the biodiesel [1];
2. The transesterification process generates a large amount of glycerol, which demand new applications [2].

Therefore, to further expansion of industry biodiesel, it is necessary to address these great drawbacks. Mainly, to develop a process to consume the glycerol converting it to products with a high value-added can contribute to reducing the cost of the biodiesel and make their production more competitive with fossil diesel. Glycerol is a coproduct of the biodiesel formed in a proportion of 10 wt. % and has become an attractive raw material with potential industrial applications [3]. Therefore, new approaches have been developed to valorize the glycerol and consequently reduce the cost of production of the biodiesel.

In addition to their high availability, glycerol is a versatile feedstock with chemical and physical properties that make him a platform molecule for numerous chemical transformations [4]. Thus, developing catalytic processes to converting glycerol to high-value chemicals has been a goal pursued by several researchers. The strategies of synthesis involve glycerol derivatives already used at an industrial scale such as glycerol carbonate, 1,2 and 1,3- propanediol, 2,3-butanediol, butanol, monoglycerides, and citric acid [5]. Moreover, glycerol is an ingredient for the synthesis of solvents, surfactants, paints, and cosmetics [6].

The production of acetals and cyclic ketals from glycerol with aldehydes and ketones, respectively, has demonstrated to be an interesting route from an industrial viewpoint, mainly because these compounds have applications as

chemical intermediates [7]. Highlighted, the solketal (*i.e.*, (2,2-dimethyl-1-3-dioxolane-4-yl)methanol) has received significant attention due to their properties as a fuel additive. Liquid catalysts such as *p*-toluenesulfonic acid are industrially used in industry for glycerol acetalization, nonetheless, this process requires heating (373 K) for long reaction time (ca. 12 h) [8]. Although inexpensive, homogeneous acid catalysts have serious drawbacks such as the high corrosiveness, the difficult to reuse, and the necessity of neutralization steps, which generate effluents and residues, being environmentally unfriendly.

The use of solid acid catalysts in reactions of condensation of glycerol with acetone may circumvent these disadvantages [9]. Moreover, these acidic solid are also used in routes to produce glycerol acetates, which is an attractive route for its valorization. The synthesized products through this pathway can be used as fuel additives, pharmaceuticals, cryogenics, and cosmetics [10]. Different processes to produce acetyl glycerides have been described in the literature, which employs acetic acid, aldehydes, or acetone as carbonylic reactants [11]. In general, the esterification of glycerol with HOAc leads to the formation of mono-, di-, or triesters [12]. The main reaction parameters are the temperature, molar ratio of reactants, and catalyst load. Although uncatalyzed processes can be also used to generate acetyl glycerides, the reaction rates are influenced by the operating conditions; generally, high temperatures are required to achieve a reasonable conversion [13]. Conversely, when a Lewis or Brønsted acid catalyst is present, the reactions are satisfactorily carried out at 333 K.

Monoterpenes are a renewable raw material found in essential oils as well as in rejects of Kraft-process of the industry of cellulose. Terpenes derivatives (terpenoids) are themselves extensively employed in producing more valuable chemicals. Terpenic alcohols as β -citronellol are valuable feedstock for the industries of fragrance, food, pharmacy, and fine chemicals [14 - 16]. β -citronellyl acetate is an important terpene ester which finds extensive applications as fragrance and perfumery ingredients, intermediate in organic synthesis process industries [16]. This valuable compound is generally synthesized through enzymatic processes or *via* Brønsted acid-catalyzed reactions [17, 18]. However, the high cost of enzymatic catalysts, and the concerns with environmental legislation, has moved the industries toward the development of new green chemistry methodologies for the synthesis of β -citronellyl acetate [19].

An interesting product obtained from terpenic alcohols are the terpinyl carbamates, which are useful in the synthesis of drugs, or in the chemical of peptides. Carbamates are an important class of compounds with various interesting properties, such as structural elements of many therapeutic agents, and agricultural chemicals [20]. Structurally, the carbamate functionality is related to

(E)-N-Methyl-1-(Methylthio)-2-Nitroethenamine (Nmsm) as a Versatile Ambiphilic Synthone in Organic Synthesis

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Abstract: (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine (NMSM) **1** is a versatile molecule that contains four active sites with three functional groups on an ethane motif. NMSM as a precursor reactant has been widely applied in the diversity-oriented synthesis of various heterocyclic motifs, *bis*-heterocyclic, fused heterocyclic and spirocyclic scaffolds. These privileged scaffolds were synthesized *via* numerous types of reactions, such as Michael addition, 1,3-dipolar cycloaddition, heteroannulation reaction and also many cascade reactions *via* multi-component reactions. Moreover, the flexibility and high reactivity of NMSM as a versatile ambiphilic synthon signify it as a suitable building block in medicinal chemistry and bulk drug synthesis. In the present book chapter, we focused on the advances in the chemistry of NMSM as an effective reagent in organic synthesis.

Keywords: Ambiphilic synthon, Bulk drugs, *Bis*-heterocyclic compounds, (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine, Fused heterocyclic compounds, Multi-component reactions, Nitroketene *N,S*-acetal, One-pot reactions, Spirocyclic compounds.

INTRODUCTION

Ambiphilic synthons, which bear both nucleophilic and electrophilic sites, have great potential in developing new synthetic routes in organic synthesis. Ketene acetals are versatile ambiphilic synthons, which bear electron-withdrawing and electron-releasing substituents, lead to inimitable structural features and earned great interest to synthetic chemists due to their significance as useful starting materials in organic chemistry [1 - 5].

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Among them, nitroketene *N*, *S*-acetal, (*E*)-*N*-methyl-1-(methylthio)-2-nitroethene (1*N*-methyl-1*S*-methyl-2-nitroethylene) (NMSM) **1** is a two-carbon synthon that contains four active sites with three functional groups on an ethane motif (Fig. 1) [6 - 8].

The three functional groups on the ethylene moiety include nitro, methylsulfanyl and methylamino, each one of which is suitable for synthetic utility and functional group manipulation. With a strong electron-withdrawing nitro group, the nitroethylene substructure in NMSM is a good Michael acceptor. The methylsulfanyl group is a good leaving group and also an electron donor. It can be substituted with a range of nucleophiles following the nucleophilic vinylic substitution (S_NV) mechanism. The methylamino group in NMSM acts as an electron donor and thus is a good Michael donor. The ethylene moiety is a polarized push-pull alkene and due to polarization, C2 exhibits nucleophilic characteristics and C1 exhibits electrophilic characteristics. These features of NMSM make it highly adaptable and simple to use in the Michael addition, annulations, cyclization and multicomponent reactions.

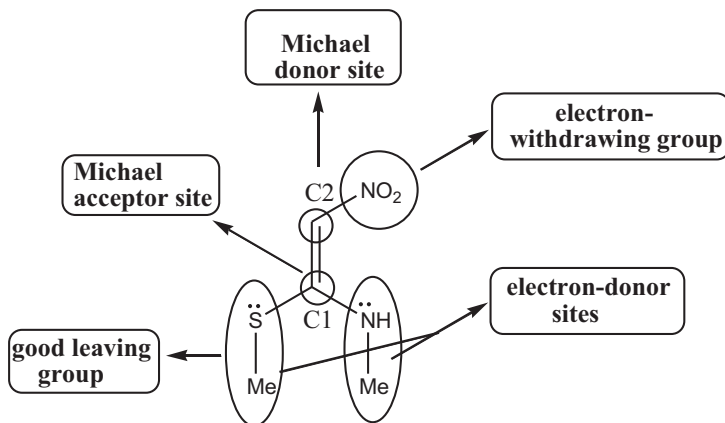
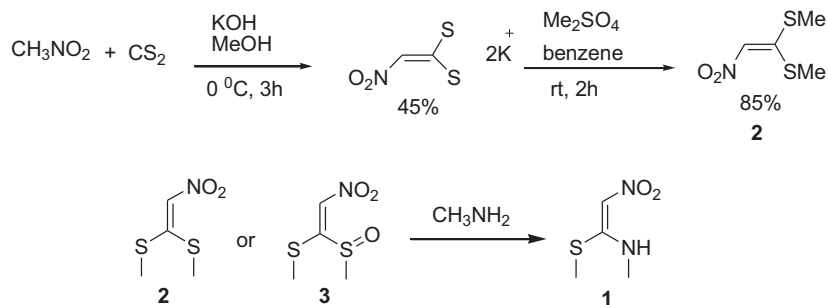


Fig.(1). The reaction profile of NMSM.

NMSM is a synthetic equivalent of nitroacetic acid and glycine. It is also used in industrial scale for the synthesis of anti-ulcer bulk drugs ranitidine [9, 10] and nizatidine [11]. NMSM participates in several commonly known reactions, such as heteroannulation reaction, 1,3-dipolar cycloaddition, Michael addition, and also several cascade reactions, to afford novel *N*-, *O*- and *S*-containing heterocycles with high regio- and stereoselectivities [12]. These qualities make NMSM a multi-faceted building block and utilized as a starting material for the construction of a variety of heterocycles. In the present book chapter, we demonstrate the chemistry of NMSM in terms of reactivity pattern, and applications in the synthesis of a range of heterocycles.

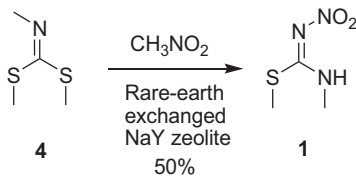
Preparation of NMSM

The key starting material in the preparation of NMSM is 1,1-bis(methylthio)-2-nitroethylene **2**. This can be synthesized by the addition of the nitromethane anion to CS₂ and methylation to give 1,1-bis(methylthio)-2-nitroethylene **2** [13 - 15]. The preparation of NMSM involves an amination of 1,1-bis(methylthio)-2-nitroethylene **2** or of the corresponding monosulphoxide **3** with methylamine (Scheme 1). A serious problem in this method is the formation of 1,1-bis(methylamino)-2-nitroethylene, by further reaction with a second molecule of methylamine.



Scheme (1). Preparation of NMSM.

To avoid this problem, another approach was adopted for the synthesis of NMSM [16, 17]. In this method, nitromethane was allowed to react with dimethyl methylcarbonimidodithioate **4** using a rare-earth (La, Pr and Sm)-exchanged NaY zeolite as a catalyst (Scheme 2).



Scheme (2). Preparation of NMSM.

APPLICATIONS OF NMSM IN THE SYNTHESIS OF HETEROCYCLES

Heterocyclic compounds exhibit rich chemistry with many applications in medicinal chemistry, organic chemistry and industry [18]. Many heterocyclic compounds exist in many natural products, such as antibiotics, hormones, vitamins and dyes [19]. It is highly enviable to design elegant, cost-effective novel methodologies for the synthesis of nitrogen-, oxygen-, and sulfur-containing heterocycles. Multi-component reactions (MCRs) are chemical transformations

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