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NOVEL METHODS OF SYNTHESIS OF HETEROCYCLIC COMPOUNDS

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ABSTRACT

Heterocyclic compounds form the structural backbone of many natural products, therapeutic agents, and functional materials. The quest for novel and efficient methods of their synthesis has become a central focus in modern organic chemistry. Recent innovations combine classical synthetic principles with advanced techniques, including metal-catalyzed cross-coupling, multicomponent reactions, organocatalysis, and biocatalytic approaches, enabling rapid and selective assembly of diverse heterocyclic frameworks. Emerging green chemistry strategies such as microwave-assisted synthesis, ionic liquids, and solvent-free conditions have further enhanced sustainability and reduced environmental impact. These methodologies not only improve atom economy and reaction efficiency but also expand the scope of accessible heterocycles with potential biological and industrial significance. This work reviews the recent progress in novel synthetic approaches, highlighting their scope, advantages, and future prospects in heterocyclic chemistry.

KEYWORDS: Food and Drug Administration, microwave-assisted synthesis.

INTRODUCTION

Hetrocyclic compound

Five member and six member heterocyclic compounds are the most inspiring, applied and largest market of the organic chemistry.1 Moreover, it empowers biologist for understanding the chemistry of biological processes, therefore it improve the quality of human life. It is the

burgeoning area of research and also maintained the leading position with excellent practical and theoretical importance since long time. Pre-eminently, conventional pharmacological agents which impersonate several natural products having pharmacological potential are also heterocycles. For that reason, medicinal chemists have consistently striving to understand the specific role of the heterocycles in counteracting the various diseases. Thereby, searching of improved pharmaceuticals for drug discovery program always been at forefront attention for researchers. Most value added atoms like nitrogen and sulfur containing heterocycles having immense importance due to its presence in several medicines which are under clinical trials for treatment of current global COVID-19 pandemic.

Recently, the U.S. Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for Pfizer's Paxlovid (nirmatrelvir tablets and ritonavir tablets, copackaged for oral use) for the treatment of mild-to-moderate corona virus disease (COVID-19).2 Most pharmaceuticals are based on heterocycles. An inspection of the structures of the top selling brand name drugs in 2007.3 Literature survey reveals that 8 of the top 10 and 71 of the top 100 drugs contain heterocycles. This is not surprising as heterocycles have dominated medicinal chemistry from the beginning. Consistent with their importance, many U.S. patents by pharmaceutical companies involve heterocyclic compounds. For example, a search of the patent literature from 1976 to September 2008 revealed that 1729 patents issued to Pfizer, as a representative company, contain the word "pyridine." Merck has 3504 U.S. patents containing the word pyridine.4 This is not peculiar to pyridine, other heterocycles in medicine; include examples of thiazole, pyrazole, quinoline, and pyrimidine in many pharmaceutically active ingredients.

Heterocycles are cyclic compounds that have at least one heteroatom as a ring component and are extremely important for medicinal and industrial applications. The most common heteroatoms are nitrogen, oxygen and sulfur, although heterocyclic rings with other heteroatoms are also widely known. Many heterocyclic compounds in biological processes have great significance. Several natural drugs are heterocycles, such as papaverine, quinine, emetine, codeine, reserpine, atropine, theophylline, morphine, and procaine. Many synthetic drugs containing heterocycles, including isoniazid, diazepam, metronidazole, chlorpromazine, barbiturate, azidothymidine, captopril, methotrexate and antipyrin. Heterocyclic compounds consisting of many life-essential biochemical materials.8 These heterocyclic natural and synthetic compounds are involved in chemical reactions within the human body. The

heterocycles are important, because they create the innovative and interesting products that enrich our society.

There is a wide range of heterocyclic compounds that are well known and isolated from different natural sources. This number is growing very high as they have gained a special position in pharmaceutically important natural products and synthetic compounds. The studies of heterocyclic motif are of enormous both from the practical and theoretical view. The heterocyclic compounds are very widespread in nature and in various aspects are important for our life. All biological processes are expressed through chemical reactions. Life's fundamental manifestations such as energy supply, nerve impulses transmission, metabolism and genetic information transfer are all based on chemical interactions involving the presence of many hetero-cyclic compounds such as enzymes, coenzymes, vitamins, adenosine triphosphate (ATP), deoxyribonucleic acid (DNA), and ribonucleic acid (RNA). Most heterocyclic compounds occur naturally and are actively involved in nucleic acids (pyrimidine and purine bases), vitamins (thiamine B1, riboflavin B2, nicotinamide B3, and pyridoxine B6), essential amino acids, chlorophyll, macrolides, cephalosporins, and penicillins.

The most of agrochemicals and pharmaceuticals are heterocyclic compounds. Heterocyclic scaffolds and their forms are the most commonly prescribed as antibiotics, antidepressants, anti-alzheimers, anti-cancers and anti-HIV.10 Heterocyclic skeleton are present in several natural and synthetic drugs. Heterocycles are found in many natural products, biomolecules, a number of medicines and biologically active compounds having antimalarial, antibiotic, anti-tubercular, antitumor, inflammatory, antidepressant, anti-HIV, anti- antiviral, antimicrobial, herbicide, and insecticide activity. Many heterocycles have important uses in material science such as fluorescent sensors, information storage, brightening agents, dyestuffs, plastics and analytical reagents. They also have applications in polymer and supra-molecular chemistry, specifically in conjugated polymers. Many of these found to be active organic conductors, semiconductors, molecular wires, organic light emitting diodes (OLEDs), photovoltaic cells, optical data carriers, light harvesting devices, chemically controllable switches and liquid crystalline compounds. Heterocycles are received much interest due to their synthetic utility as synthetic precursors, chiral auxiliaries, protecting groups, organocatalysts and metal ligands in asymmetric catalysts in organic synthesis.

Pyrimidines and purines, building blocks of DNA and RNA are nitrogen containing heterocycles which are directly involved in the maintenance of genetic codes used in the development and functioning of all living organisms.[11] Moreover, vitamins of the B group, e.g. vitamin B7 (Biotin)12 are nitrogen rich and vitamin C (L-Ascorbic acid) and vitamin E (α-Tocopherol) are oxygen containing heterocycles. Additionally, essential amino acids like proline, histidine and tryptophan, some hormones as well as chlorophyll and hemoglobin14 are excellent examples of heterocycles.

Drugs are the chemical entities that are used to cure various diseases and to prevent them. Several potent bioactive drugs are available in market which containing heterocyclic fragment and some of them are represented in. Delavirdine is a nonnucleoside reverse transcriptase inhibitor (nNRTI) with activity against Human Immunodeficiency Virus Type 1 (HIV-1). Isoniazid is used to treat and to prevent tuberculosis (TB). Omeprazole used in the treatment of gastro esophageal reflux disease, peptic ulcer disease and Zollinger-Ellison syndrome. Losartan is a medication mainly used to treat high blood pressure. Voriconazole is a triazole antifungal medication used to treat serious fungal infections. Triazolam is used to treat insomnia. Celecoxib is a non-steroidal anti-inflammatory drug. Sildenafil is used to treat erectile dysfunction and pulmonary arterial hypertension. Allopurinol is used to treat gout and certain types of kidney stones.

MATERIAL AND METHOD

General Method

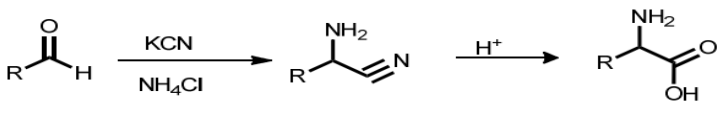
^{1}H NMR spectra were recorded at 500.20 MHz, while the ^{13}C NMR spectra were measured at 125.62 MHz in $CDCl_3$ or in DMSO-d6 at ambient temperature, with a Bruker AV NEO Ascend 500 spectrometer (Bruker Biospin, Karlsruhe, Germany) with Double Resonance Broad Band Probe (BBO). Chemical shifts are given, relative to tetramethysilane (TMS) as internal standard, in δ (ppm). Elemental analyses were performed with a Perkin–Elmer CHNS-2400 Ser II Elemental Analyzer. Microwave-promoted reactions were carried out in sealed reaction vials (10 mL) in a microwave (CEM, Discover, SP) cavity (CEM Corporation, Matthwes, NC, USA). Optical rotations were measured with a Perkin–Elmer 341 polarimeter (Perkin–Elmer, Shelton, CT, USA). Melting points were determined with a Hinotex-X4 micro melting point apparatus (Hinotek, Ningbo, China) and are uncorrected. Racemic *diendo*-and *diexo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acids (±)-**2** and (±)-**11** were prepared according to a literature procedure.

The enantiomers of 2-aminonorbornene esters (+)-**1**, (−)-**1**, (+)-**10** and (−)-**10** were prepared from racemic 2-aminonorbornene esters via diastereomeric salt formation with *O,O′*-di-*p*-toluoyltartaric acid (DPTTA) and *O,O′*-dibenzoyltartaric acid (DBTA) as previously published. The *ee* values of (+)-**1** and (−)-**1** were determined by a literature method. The *ee* values for (+)-**10** (92%) and (−)-**10** (98%) were determined by HPLC using Phenomenex-IA column after derivatization with benzoyl chloride in the presence of TEA. Analytical conditions were as follows: eluent: a mixture of *n*-hexane and isopropyl alcohol (IPA) (70:30), flow rate: 0.3 mL·min^{-1}, detection at 254 nm, retention times: (−)-10: 40.81 min (antipode: 25.33 min). The *ee* values for (−)-4 (98%), (+)-4 (95%), (−)-13 (95%) and (+)-13 (96%) were determined by GC on a Chirasil-L-Val column (25 m): 180 °C isotherm, 1 mL·min^{-1}, retention times (−)-13: 4.91 min, (+)-13: 4.52 min; flow rate 1 mL·min^{-1}, 160 °C for 5 min → 180 °C (rate of temperature rise 10 °C/min; retention times (−)-4: 11.84 (min), (+)-4: 12.64 (min). The *ee* values of the domino ring closure compounds (−)-6 and (+)-6 were identified by HPLC using Chiracel-OD-H column, eluent: a mixture of *n*-hexane and IPA (70:30), flow rate: 0,15 mL·min^{-1}, detection at 254 nm, retention times (−)-6: 61.83 min, (+)-6: 66.29 min. The *ee* values of the domino ring closure products (−)-15 and (+)-15 were identified by HPLC using Phenomenex-IA column, eluent: a mixture of *n*-hexane and IPA (60:40), flow rate: 1 mL·min^{-1}, detection at 254 nm, retention times (−)-15: 22.04 min, (+)-15: 42.99 min. The *ee* values of the RDA products (−)-8 and (+)-8 were determined by HPLC using Phenomenex-IA column, eluent: a mixture of *n*-hexane and IPA (70:30 containing 0.1% DEA), flow rate: 0.5 mL·min^{-1}, detection at 254 nm, retention times (−)-8: 80.88 min, (+)-8: 76.58 min. The *ee* values of RDA products (−)-9 and (+)-9 were determined by HPLC using ChiralPak-IA column, eluent: a mixture of *n*-hexane and IPA (60:40 containing 0.1% DEA), flow rate: 0.5 mL·min^{-1}, detection at 254 nm, retention times (−)-9: 26.76 min, (+)-9: 23.87 min.

Multicomponant Synthesis Reaction

Strecker's amino acid synthesis

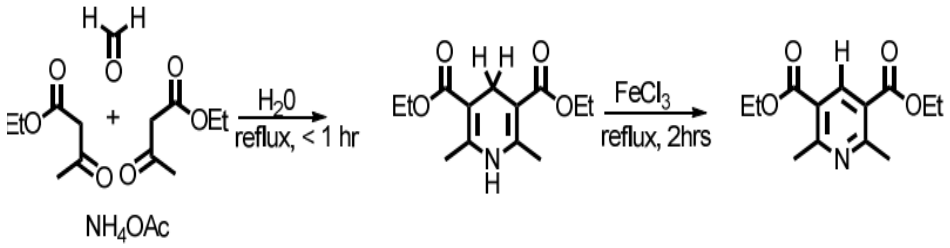
Strecker synthesis is a preparation of α-aminonitriles, which are versatile intermediates for the synthesis of amino acids by the hydrolysis of nitriles as shown in the scheme-.[1]



Scheme- 2

Hantzsch reaction

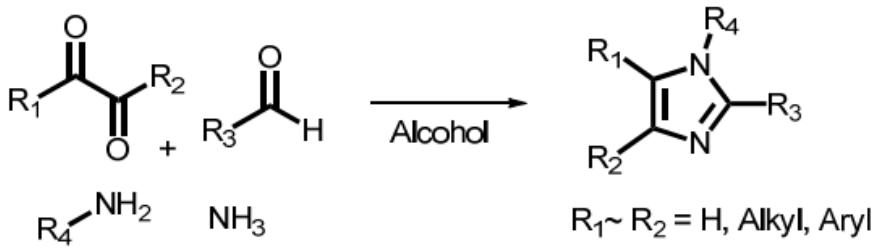
In 1882, Arthur Rudolf Hantzsch, a German chemist reported a cyclo condensation between ethyl acetoacetate, aldehyde and aqueous ammonium hydroxide to afford a heterocyclic system of 1, 4-dihydropyridine. Since then it became familiar as Hantzsch reaction.[12]



Scheme: 2

Radzisewski Imidazole Synthesis

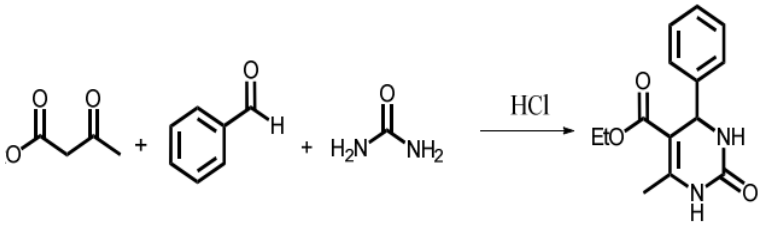
Radziszewski, in the year 1882, synthesized imidazole derivatives by condensing 1, 2-diketones with formalin, primary amine and ammonia. This is a four component reaction as shown in the scheme-3.[13]



Scheme: 3

Biginelli reaction

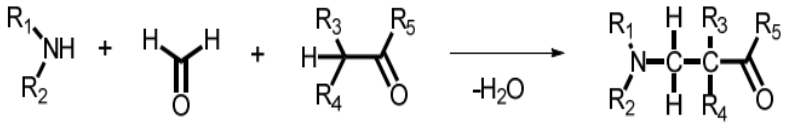
In 1891, an Italian chemist, Pietro Biginelli developed a methodology for multicomponent condensation reaction in which ethyl acetoacetate, aldehyde and urea were reacted in acidic medium in ethanol to afford the corresponding heterocyclic product, 3,4- dihydropyrimidin-2(1*H*)-one as shown in the scheme-4



Scheme: 4

Mannich reaction

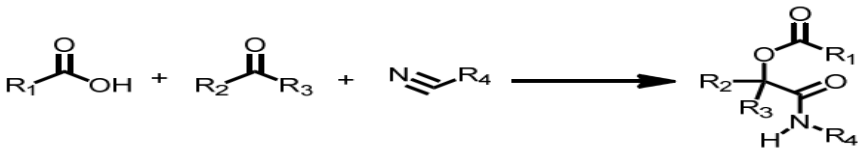
In 1912, Carl Mannich, introduced a new methodology for carbon-carbon and carbonnitrogen bond formation in one pot by the condensation of aldehyde, amine and active methylene containing keto compounds to give the corresponding derivatives as shown in the scheme-4.[4]



Scheme: 5

Passerine reaction

In 1920's Passerini disclosed the utility of isocyanides with the creation of α- acyloxyamide from the condensation of a carboxylic acid, an aldehyde, and an isocyanide as shown in the scheme-8.[4] This reaction was the first MCR of isonitriles.

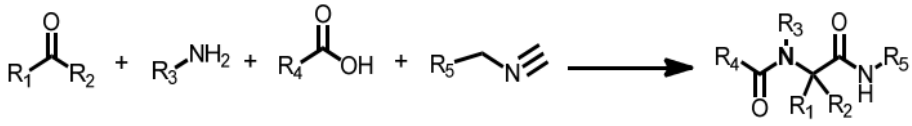


Scheme: 6

The first isocyanide was prepared in 1859, but they were not available for a whole century, since all the now known methods of preparing isocyanides did not exist. Therefore, and due to the intense bad smell of the isocyanides, their chemistry remained a rather neglected part of organic chemistry.

Ugi reaction

Ivar Karl Ugi, in 1959 introduced a four component reaction, which involves the generation of α-N-acylaminoamide from the condensation of an aldehyde, carboxylic acid, isonitrile and a primary amine as shown in the scheme-11.[5] The reaction has been the most extensively studied and applied MCR in the drug discovery process.[5]



Scheme: 7

In 1958, the isocyanides became available by dehydrating the *N*-formyl amines and since then this chemistry has been increasingly active. One year later the four component reaction of the isocyanides was introduced and from 1962 this is referred to as the Ugi-4-component reaction (U-4CR). The U-4CR and its combinations with further reactions is nowadays a very active part of organic chemistry. In1963, Mc Farland[16] found that the courses of U-4CRs depend very much on their reaction conditions. Even the concentration of their products can strongly interfere with the course of U-4 MCRs.

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