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A Review of Synthetic Approaches and Biological Activity of Substituted Hydrazones

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Abstract

Hydrazone derivatives are used extensively in organic synthesis. The reactive parts of these molecules are the carbon and nitrogen atoms. Hydrazones are used to synthesize heterocyclic compounds possessing biological activities. They exhibit cardio-protective, anti-oxidant, anti-inflammatory, anti-convulsant, anti-microbial, anti-cancer, anti-protozoan, anti-parasitic, anti-platelet, anti-helminthic, anti-diabetic, anti-tubercular and anti-HIV properties. In recent years, there have been numerous developments in this field and many new aspects of hydrazone chemistry and applications have been developed.

Keywords: ***Anti-Diabetic, Anti-Tubercular, Hydrazone***

Introduction

Substituted hydrazones are of interest due to their biological activities and their use as metal chelating agents [1]. Hydrazone derivatives are used as drugs for the treatment of tuberculosis, leprosy, and mental disorders [2]. Hydrazones capable of forming Schiff bases are used as metal extracting agents as well as for characterization of certain transition metals by spectroscopy [3-6]. The hydrazones in which X and Y functionalities are CO_2R or CN are useful for synthesis of dyes [7-9]. The lone pair of electrons on the nitrogen makes the carbon of the hydrazone both electron rich and nucleophilic [10].

Hydrazones possess the general chemical structure $R_1R_2C=NNR_3R_4$ [11-12]. Both the nitrogen atoms of hydrazone possess nucleophilic activity but the amino type nitrogen is more reactive. The carbon atom serves as both a nucleophile as well as electrophile. Hydrazones are typically prepared by the reaction of hydrazine with carbonyl compounds such as aldehydes or ketones [13-14].

Synthetic Use of Hydrazones

Hydrazones act as reactants in various reactions such as Barton Hydrazone Iodination, Bamford-Stevens reaction, Shapiro reaction, etc. to form vinyl compounds. They are intermediates in Wolff-Kishner reduction. They are also used for the formation of alkenes in the Eschenmoser reaction. Tosyl and Boc-hydrazones are effective nucleophiles in the Mitsunobu reaction (**FIG. 1)** [15].

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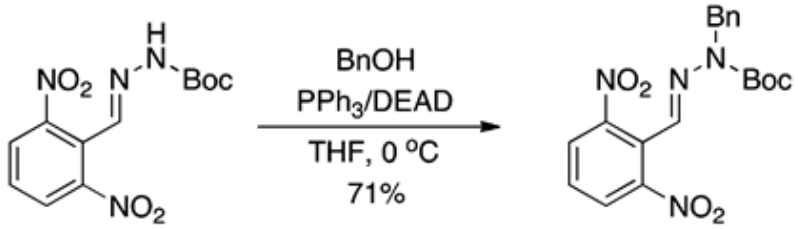

FIG. 1. **Use of a Boc-hydrazone for Mitsunobu reaction**

Generally, Arylhydrazones serve as substrates in Fisher Indole synthesis. In the presence of a catalyst, Arylhydrazones undergo Claisen rearrangement and elimination of Ammonia to provide the Indole ring (**FIG.2)** [16].

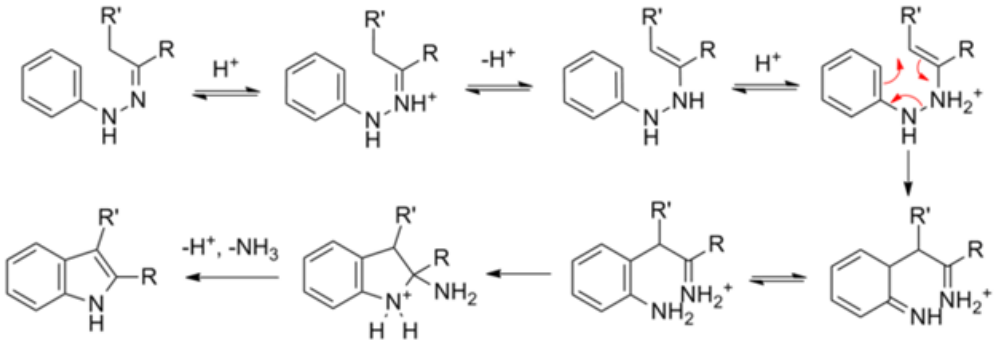

FIG.2. **Use of a hydrazone to synthesize the Indole ring**

Hydrazones, because of the presence of the functional group C=N, have been used for free radical-induced cyclizations also (**FIG.3)** [17-18].

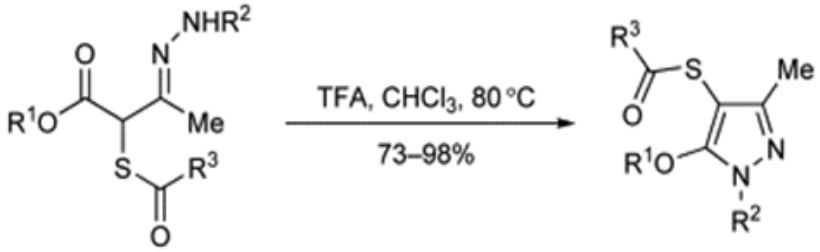

FIG. 3. **Use of the functional group C=N, for free radical-induced cyclization**

Synthesis of Heterocycles

Heterocyclic compounds are found in many natural products such as antibiotics, hormones, vitamins, etc. The synthesis of N-containing heterocycles is of great importance in modern science. A great number of heterocyclic rings containing 1-4 nitrogen atoms can be accomplished by hydrazine and hydrazones making this a good approach for developing intermediates for pharmaceuticals, dyes and agrochemicals [19-21]. Commonly synthesized heterocycles from hydrazone derivatives are:

(i) Pyrazoles:

A conventional method to obtain pyrazoles is by a ring transformation reaction shown as (**FIG.4)** [22]:

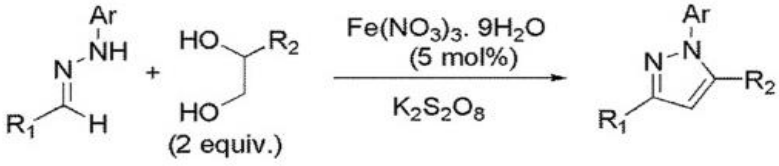

FIG. 4. **Synthesis of Pyrazoles by ring transformation reaction.**

(ii) Triazoles:

A triazole refers to any of the heterocyclic compounds with molecular formula $C_2H_3N_3$, having a five-membered ring of two

carbon atoms and three nitrogen atoms. A series of 1,2,4-triazoles have been prepared by the use of hydrazones (**FIG. 5**) [22]:

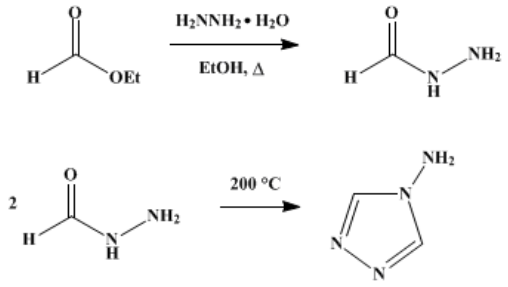

FIG. 5. **Synthesis of 1,2,4-Triazoles**

(iii) N-Aminoazacycloalkanes:

These are heterocyclic compounds containing hydrazine moiety and are extensively used as drugs, pesticides and precursors in organic synthesis (**FIG. 6**) [23]:

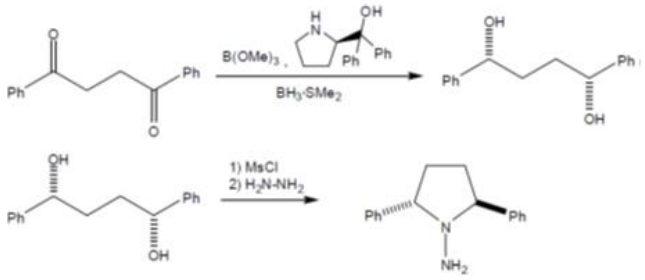

FIG. 6. **Synthesis of N-Aminoazacycloalkanes**

(iv) Pyrazolidine homologs:

Pyrazolidines are heterocyclic compounds containing an N-N bond. They have been successfully synthesized enantioselectively using the methodology (**FIG. 7**) [24]:

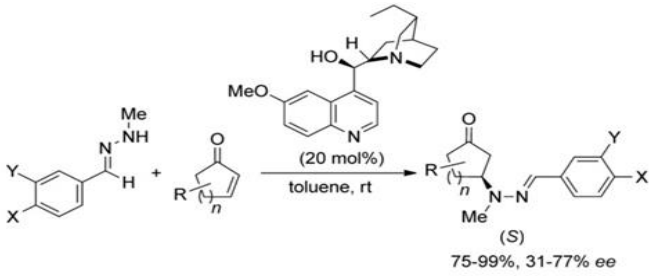

FIG.7. **Synthesis of Pyrazolidine homologs**

(v) Piperazic acid derivatives:

Hydrazone derivatives have been used to synthesize Piperazic acid or Hexahydropyridazine-3-carboxylic acid compounds (**FIG. 8**) [25]:

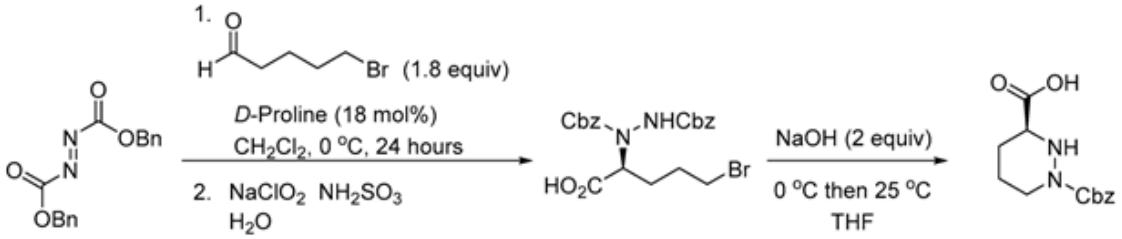

FIG.8. **Synthesis of Piperazic acid derivatives**

Biological activity

Hydrazones are known to possess anti-microbial, anti-convulsant, analgesic, anti-inflammatory, anti-platelet, anti-tubercular and anti-tumor activities (**FIG. 9**) [26,27]. Nifruoxazide is known for antimicrobial activity against S. aureus and has been found to be active at concentrations of 0.16-63.00 µg/mL. Some studies have shown that acetyl hydrazones provide good protection against convulsions. Arylidene hydrazides such as Iproniazide, Isocarboxazide and Nialamide are useful as anti-depressants and act by inhibiting the enzyme, Monoamine Oxidase. The aroyl hydrazone chelator, 2-hydroxy-1-naphtthylaldehyde isonicotinoyl hydrazine, possesses anti-malarial activity. Isonicotinic acid hydrazide has in vivo inhibitory activity towards M. tuberculosis bacterium. Another compound, N′-(1-{1-[4-nitrophenyl-3-phenyl-1H-pyrazole-4-yl}methylene)-2-chlorobenzohydrazide shows anti-cancer activity (**FIG. 10**).

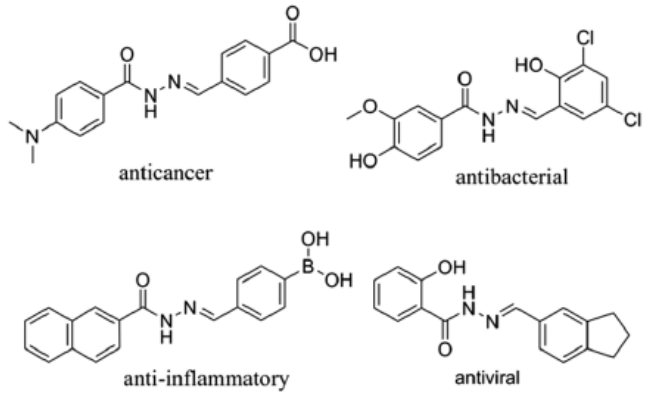

FIG. 9. **Biological activities of various hydrazones**

Future Directions

The hydrazone functional group is useful for achieving many chemical transformations. At present, hydrazones have been used mainly as surrogates for the diazo group. However, the future application of hydrazones can also involve sigmatropic rearrangements, ene–yne metathesis, C−H bond insertion, ylide synthesis, and cross-coupling reactions. A future pharmacological application of hydrazones is in drug delivery via site-specific drug release in tumor tissue or for use in the cases of thrombosis. Many studies are investigating strategies to synthesize hydrazones for this application, using heat and chemical catalysts.

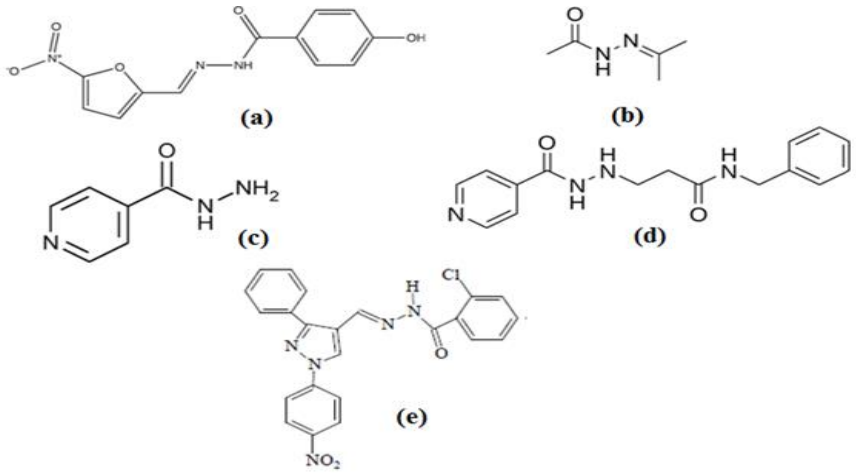

FIG.10. **The chemical structures of (a) Nifruoxazide (b) Acetylhydrazone (c) Nialamide (d) Isoniazid (e) N′-(1-{1-[4-nitrophenyl-3-phenyl-1H-pyrazole-4-yl}methylene)-2-chlorobenzohydrazide**

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