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Properties and Uses of Substituted Hydrazones

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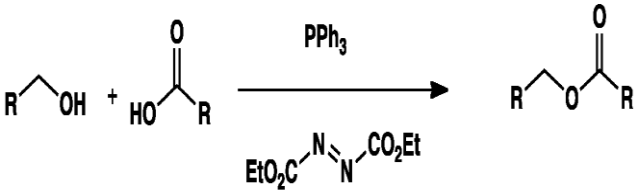
Abstract: Substituted hydrazones have been used extensively in organic synthesis. The active centers of a hydrazone are the carbon and nitrogen atoms which are mainly responsible for their physical and chemical properties. due to their reactivity toward electrophiles and nucleophiles, hydrazones are used for the synthesis of heterocyclic compounds having a variety of biological activities. Hydrazones and their derivatives are known to exhibit a wide range of biological activities such as anti-oxidant, anti-inflammatory, anti-convulsant, analgesic, anti-microbial, anti-cancer, anti-protozoal, anti-parasitic, anti-platelet, cardio-protective, anti-helminthic, anti-diabetic, anti-tubercular, anti-HIV, and so forth. In recent years, there have been considerable developments in this field and many new aspects of hydrazone chemistry and many applications have evolved.
Keywords: Hydrazine derivatives, substituted hydrazones, heterocyclization, diazo group**.**

1 Introduction

The properties of substituted hydrazones are of interest due to their biological activities and their use as metal extracting agents [1]. Hydrazone derivatives are used as fungicides and as drugs in the treatment of diseases such as tuberculosis, leprosy, and mental disorders [2]. Schiff base hydrazones are widely used in analytical chemistry as selective metal extracting agents as well as for spectroscopic determination of certain transition metals [3,6]. The hydrazones in which X and Y functionalities are CO_2R or CN, are extremely important for synthesis of dyes [7,9]. The nitrogen lone pair makesthe hydrazone carbon atom electron rich so that it can act as a nucleophile[10].
Hydrazones have the chemical structure of $R_1R_2C{=}NNR_3R_4$ [11,12]. Both the nitrogen atoms of hydrazone are nucleophilic but the amino type nitrogen is more reactive.The carbon atom is both nucleophilic as well as electrophilic.
Hydrazonesare frequently usedfor the synthesis of heterocyclic compounds [13,14]. The general method for the synthesis of the hydrazones is by reaction of hydrazine with carbonyl compounds such as aldehydes or ketones in solvents like ethanol, methanol and butanol [15,16].

1.1 Synthetic Utility of Hydrazones

Hydrazones act as reactants in various important 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-hydrazonesare effective nucleophiles in the Mitsunobu reaction [17]:



Generally, aryl hydra zones serve as substrates in Fisher Indole synthesis. In the presence of a catalyst, ary lhydra zones undergo Claisen rearrangement and elimination of ammonia to give the Indole ring [18].
Hydrazones, because of the functional group C=N, have been used for free radical-induced cyclizations also [19][20].

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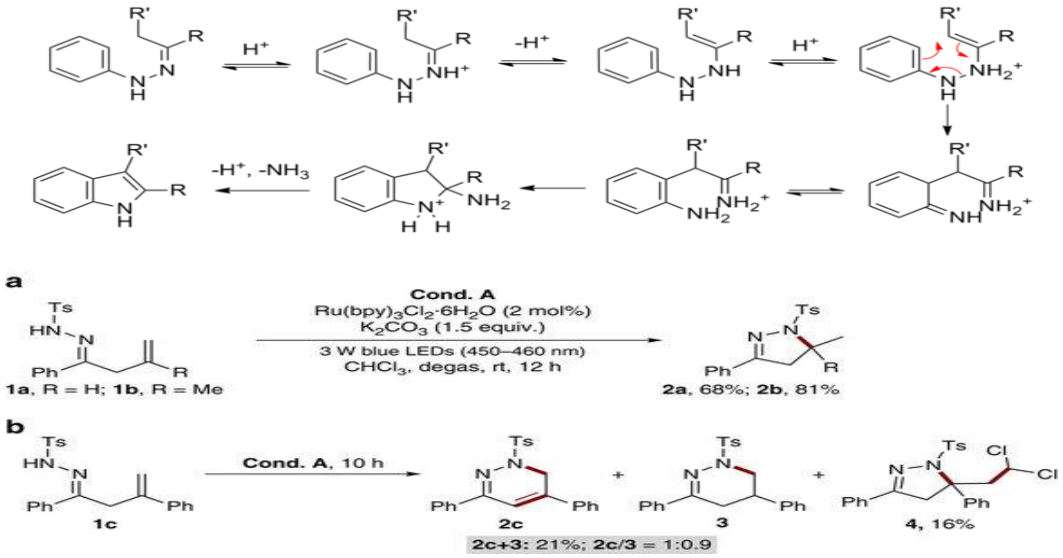


1.2 Heterocyclizations

Heterocyclic compounds are abundant in nature. Their structural subunits 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 fertile field for investigation towards developing intermediates for pharmaceuticals, dyes and agrochemicals [21][22][23]. Commonly synthesized heterocycles from hydrazone derivatives are:

1.2.1Pyrazoles

A conventional method to obtain pyrazoles by a ring transformation reaction is shown as [24]

1.2.2Triazoles

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 use of hydrazones [24].

1.2.3 N-Aminoazacycloalkanes

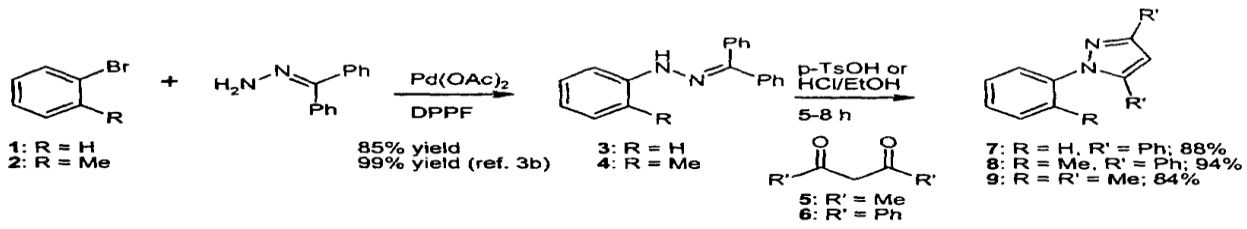
These are heterocyclic compounds containing hydrazine moiety and they have been of great interest in recent years. These heterocycles are extensively used as drugs, pesticides and precursors in organic synthesis [25].

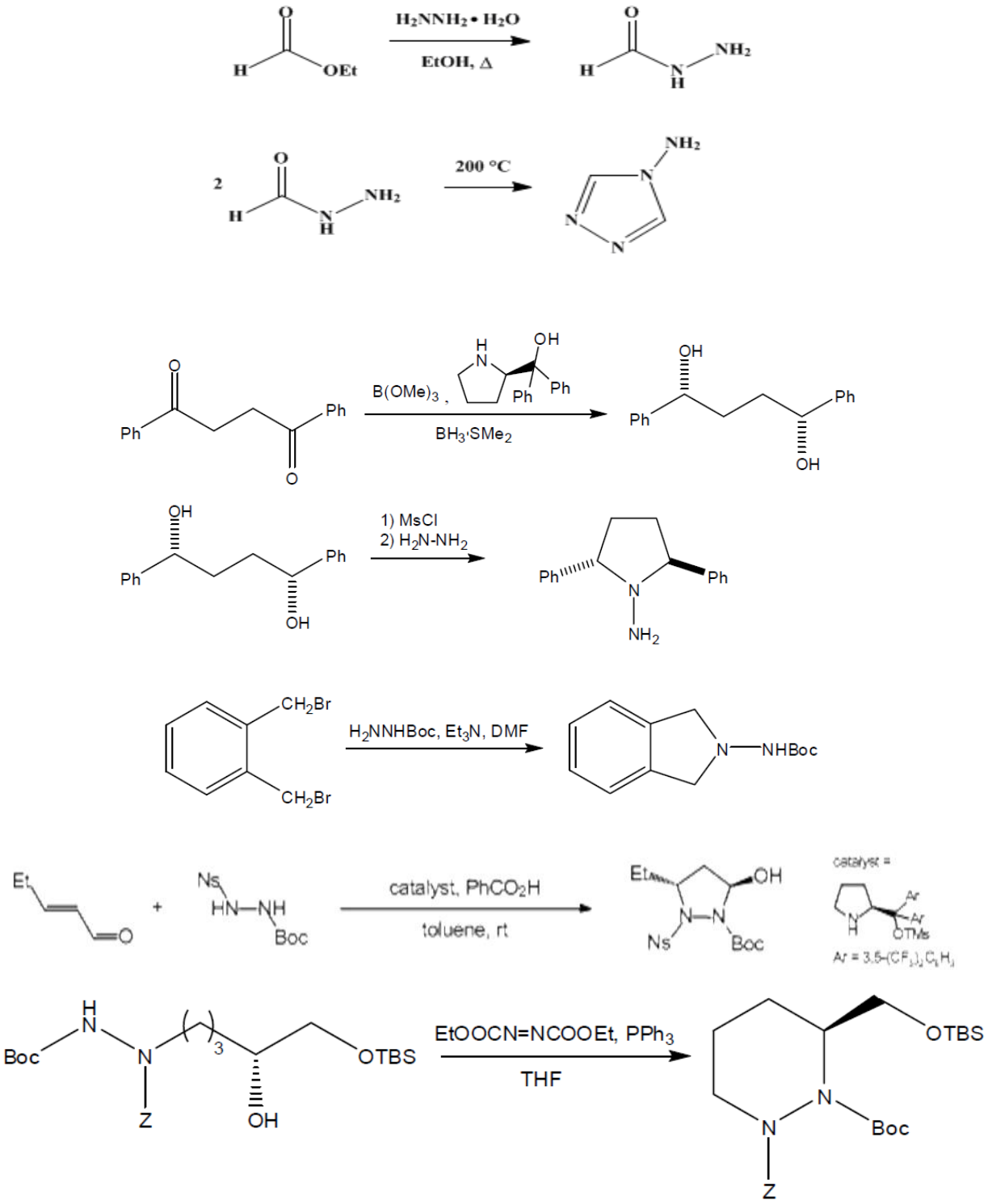
1.2.4 Pyrazolidine Homologs

Pyrazolidines are heterocyclic compounds containing an N-N bond. They have been successfully synthesized using the methodology [26]

1.2.5 PiperazicAcid Derivatives

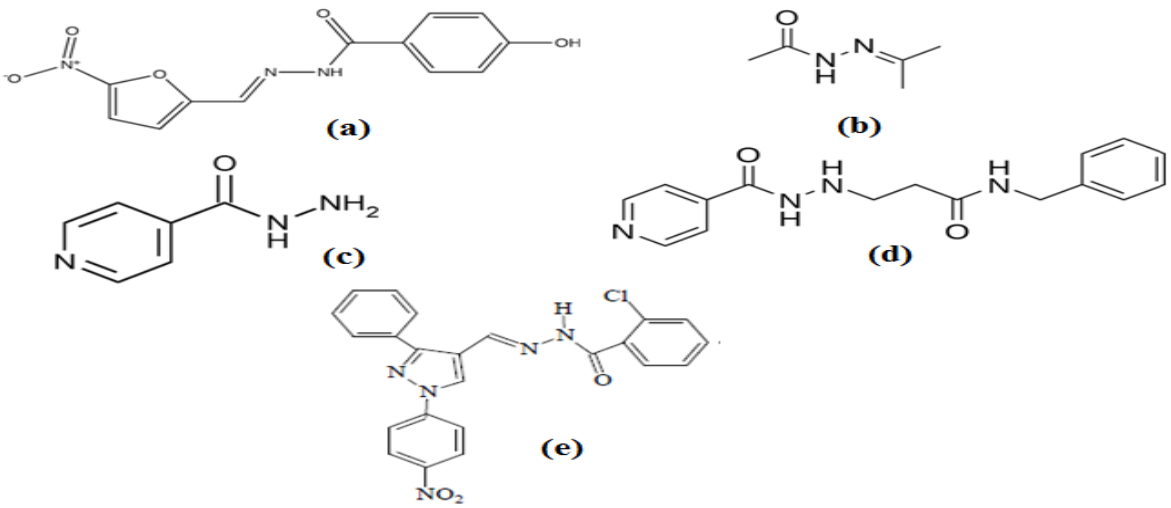
Piperazic acid or hexahydropyridazine-3-carboxylic acid derivatives have been synthesized [27].





1.3 Biological Activity

Hydrazonesare known to have anti-microbial, anti-convulsant, analgesic, anti-inflammatory, anti-platelet, anti-tubercular and anti-tumoral activities [28]. Nifruoxazide is known for antimicrobial activity against *S. aureus* and found to be active at concentrations of 0.16-63.00 µg/mL. Biological results reveal that acetylhydrazones 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 aroylhydrazonechelator, 2-hydroxy-1-naphthaldehydeisonicotinylhydrazine,has anti-malarial activity. Isonicotinic acid hydrazide has *in vivo* inhibitory activity towards *M. tuberculosis* H37Rv and *N′*-(1-{1-[4-nitrophenyl]-3-phenyl-1H-pyrazol-4-yl}methylene)-2-chlorobenzohydrazide has anticancer activity (Scheme 1).



Scheme 1. 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

Future Direction

The hydrazone functional group allows for many functional group transformations. At present, hydrazoneshave been used mainly as surrogate for thediazo group.However, a future application of hydrazones is in sigma tropic rearrangements, ene–yne metathesis, C−H bond insertion, ylide synthesis, and cross-coupling reactions.

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