Egypt. J. Chem. **Vol. 66,** No. SI 13 pp. 2371 - 2378 (2023)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Insight into the Synthesis, Biological Impact and Convenient Routes of Hydrazonoyl Halides for Synthesis of Novel Bioactive Heterocycles: Mini-Review

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Abstract

The present survey review focuses on the synthetic methods of hydrazonoyl halides published during the past 20 years. The review covers also the pharmaceutical and biological activities of some hydrazonoyl halides. Additionally, the review discussed the utilization of hydrazonoyl halides in preparation of new bioactive heterocyclic compounds.

Keywords

Hydrazonoyl halides, pharmaceutical importance, synthetic methods, chemical reactions.

1. Introduction

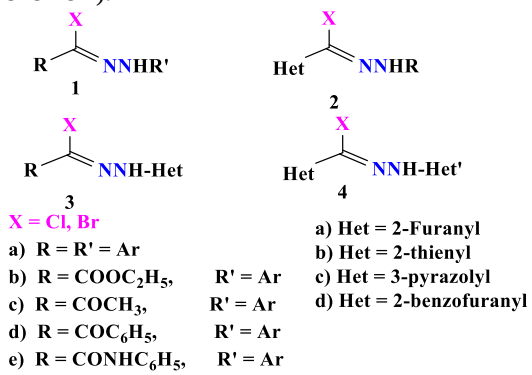
Hydrazonoyl halides are closely resembled to the other imidoyl halides. Fusco and his research group have been utilized hydrazonoyl halides to prepare a variety of pyrazole derivatives. On the other hand, Huisgen and his research group have been utilized this group of compounds to synthesize the highly active nitrile imides by treatment of hydrazonoyl halides with base. The latter were reacted as 1,3-dipoles with a wide range of different substrates to form the corresponding five-membered heterocyclic ring systems, which are mostly quite difficult to be synthesized by other methods [1-7].

Beside the *N*-arylhydrazonoyl halides, number of *N*-substituted derivatives, as *N*-carboxylic acid compounds, have been synthesized. Since the investigation of the hydrazonoyl halides (**1**) they become an important class of intermediates, particularly for the synthesis of new heterocyclic derivatives. Despite several reports covering the reactions of the hydrazonyl halides (**1**) have been published, the chemistry of them characterized by the structural formulae **2-4** has received little attention [8-11] (**Scheme 1**).

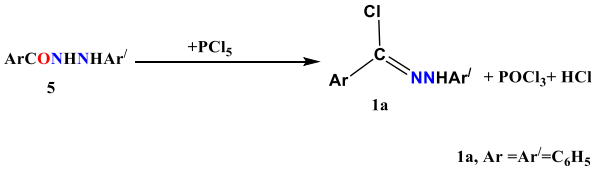
2.0 SYNTHESIS OF HYDRAZONOYL HALIDES

1.2. From Carboxylic Acid Hydrazide

The traditional method for the synthesis of hydrazonoyl halides is the reaction of the carboxylic acid hydrazide with phosphorus penta chloride [8, 12] (**Scheme 2**).



Scheme 1: Chemical structure of hydrazonoyl halides



Scheme2: Synthesis of hydrazonoyl halides from carboxylic acid hydrazide

This reaction can be performed either by using inert solvents such as methylene chloride, ether, carbon tetrachloride or chloroform or under solvent free conditions and the yields are quite good.

Wolkoff and his research group have been synthesized the hydrazonoyl chloride **1a** by the reaction of triphenylphosphine-carbontetrachloride (Ph_3P-CCl_4)

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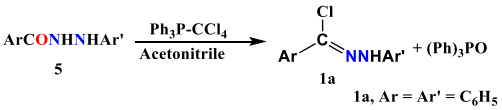
Receive Date: 16 November 2023, Revise Date: 31 December 2023, Accept Date: 03 January 2024

DOI: 10.21608/EJCHEM.2024.249272.8883

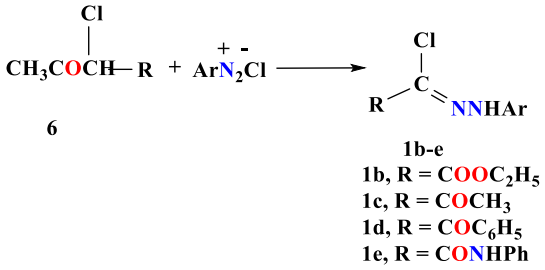
with carboxylic acid hydrazide **5** in acetonitrile (**Scheme 3**).



Scheme 3: Synthetic procedure of the hydrazonoyl chloride **1a**

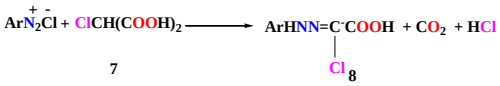
1.3. FROM DIAZONIUM CHLORIDES

Coupling of diazonium chloride with the appropriate activated halogenated methylene groups is an adequate route for the synthesis of a number of hydrazonoyl halides. Dieckmann, Favrel, Platz and others have been used this method to produce the carbo-alkoxy, carboxyl, acetyl and carbonyl derivatives [13-17] (**1b-e**)(**Scheme 4**).



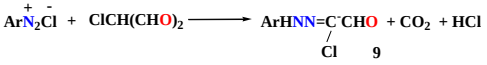
Scheme 4: Synthesis of hydrazonoyl halides from diazonium chlorides

Treatment of diazonium chlorides with chloromalonic acid **7** affording the free carboxylic acid **8** [8, 18-22] (**Scheme 5**).



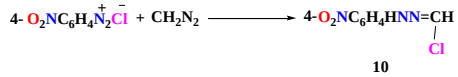
Scheme 5: synthetic procedures of the carboxylic acid **8**

Analogously, the aldehyde **(9)** was prepared by the reaction of arenediazonium chloride and chloromalonaldehyde [23] (**Scheme 6**).



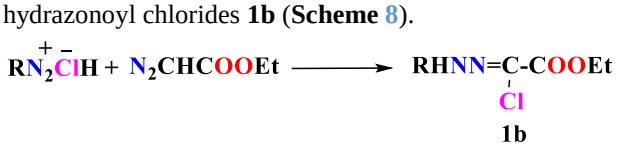
Scheme 6: Synthetic procedures of compound **9**

The hydrazonoyl chloride **10** was prepared via the reaction of 4-nitrobenzenediazonium chloride with diazomethane in excellent yield 81% [8, 24-31] (Scheme 7).



Scheme 7: Synthetic procedures of the hydrazonoyl chloride **10**

By the same method ethyl diazoacetate was reacted with diazonium chlorides to give ethoxycarbonyl hydrazonoyl chlorides **1b** (**Scheme 8**).

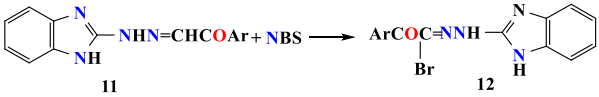


Scheme 8: Synthetic procedures of carboxyarylhydrazonoyl chlorides **1b**

1.4. FROM ALDEHYDE HYDRAZONES

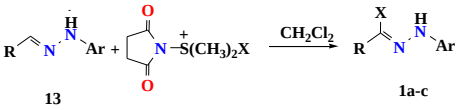
An excellent method for the synthesis of hydrazonoyl halides is the direct halogenation of arylhydrazones (aromatic or aliphatic aldehydes) with the appropriate halogen in glacial acetic acid. This method has been used also for the preparation of hydrazonoyl halides of types **2-4** [32, 33].

Hydrazonoyl bromides **12** were also synthesized by the reaction of hydrazone **11** with *N*-bromosuccinimide under reflux in dry carbon tetrachloride [34-36] [37](**Scheme 9**).



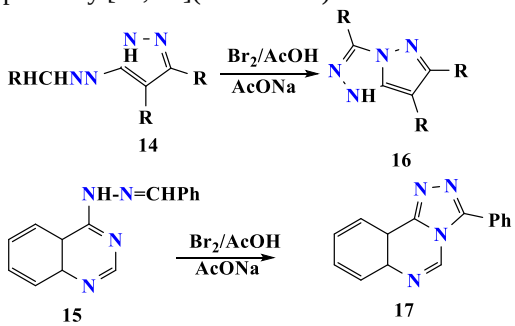
Scheme 9: Synthesis of hydrazonoyl bromide **12**

Patel and his research group introduced a convenient new method for the generation of hydrazonoyl halides. On treatment of the hydrazone **13** with *N*-bromo -or *N*-chlorosuccinimide-dimethylsulfide resulted in the formation of the corresponding hydrazonoyl halides (**1a-c**)in excellent yields [38, 39] (**Scheme 10**).



Scheme 10: Synthesis of the hydrazonoyl halides (**1a-c**)

Bromination of aldehyde N-heteroarylhydrazones **14** and **15** in acetic acid in the presence of sodium acetate, sometimes leads to intramolecular cyclization of initial hydrazonoyl bromides to yield the corresponding cyclized products **16** and **17** respectively [21, 40](**Scheme 11**).



Scheme 11: synthetic procedures of compounds **16** and **17**

3. The Applications of Hydrazonoyl Halides

3.1. Biological activity

Hydrazonoyl halides have acquired conspicuous significance since 1882 owing to their wide spectrum of biological and pharmaceutical importance and have many applications in the pharmaceutical and industrial areas [41-43].

3.1.1. Anthelmintic activity

N-Phenylbenzohydrazonoyl chloride (4-$MeC_6H_5C(Cl)=NNH–C_6H_5$) is the first hydrazonoyl halide exhibited strong activity against gastrointestinal cestoda and nematode. However, *N*-(4-chlorophenyl)-4-methoxybenzohydrazonoyl chloride (4-$MeOC_6H_5C(Cl)=NNH–C_6H_4Cl$-4) utilized for the treatment of parasitic worms in sheep. N-phenyl 4-methylbenzenecarbohydrazonoyl chloride exhibited significant effect against gastrointestinal nematodes and ovines cestodes yielding only oral quantity of 30–50 mg/kg. After 10 days of treatment in sheep anorexia and mild diarrhea occurred, these symptoms take 4-5 days to disappear. After one week from the beginning of the treatment no ill signs were observed. Consequently, N-(4-Chlorophenyl)-4-methoxybenzenecarbohydrazonoyl chloride has analogously stayed utilized against anthelmintic strongly [41, 44, 45].

3.1.2. Antiviral activity

Different N-aryl-2-aryl-2-oxo-ethane hydrazonoyl bromides derivative revealed strong antiviral activities[41, 45-47].

3.1.3. Antimicrobial activity

The types of hydrazonoyl halides which have the structure **(**Y-C_6H_4-C(X)=NNH-$C_6H_3R'R''$-2,4; Y=H, 4-Br, 4-F, 4-Cl, 3-O_2N, 4-O_2N; X=Cl or Br)**,** (Me-CO-C(Cl)=NNH-$C_6H_3R'R''$-2,4; R′= H, Br, O $_2$N; R″=H, Br, Cl, O_2N, H_2NSO_2) and **(**R-C(X)=NNH-$C_6H_3R'R''$-2,4; R: Me, Et, Pr; X: Cl or Br) were reported for their fungi static, bactericidal and toxicity activities. They exhibited fungicidal activity depending on the acid rest R. In addition, cyanomethane hydrazonoyl chlorides **(**NC-C(Cl)=NNH-C_6H_4X; X: a, H; b, Cl; c, Br; d, I; e, O_2N; f, Ac-$NHSO_2$; g, EtO-CO) utilized against wheat stem rust, phytophora poison of tomatoes and cucumber dry rust[48, 49].

3.1.4. Phytotoxicity activity

N-(4-substituted phenyl)-3-bromo-2-oxopropanehydrazonoyl bromides (Br-CH_2-COC(Br)=NNH-C_6H_4X, X = 4-Me, 4-Cl, 4-O_2N) and 3-pyridinio bromide ([$C_5H_5N^+$-C(Cl)=NNH-C_6H_4X] Br^-; X = 4-Me, 4-Cl, 4-O_2N) were examined for their ability to control plant growing at different concentrations. N-(4-nitrophenyl), N-(4-methylphenyl) and N-(4-chlorophenyl) substituents reduced the growing of roots, leaves and stalks of oats and lettuce [50, 51].

3.1.5. Pesticides

N-Aryl 2-oxoethanehydrazonoyl chlorides **(**OCH-C(Cl)=NNH-Ar) and their thioketal and ketal derivatives exhibited significant pesticide effects [51, 52].

3.1.6. Insecticidal activity

N-Aryl-2-oxopropanehydrazonoyl chlorides **(**Me-CO-C(Cl)=NNH-C_6H_3RR' ; R: 2-Me-, H-, 2-Cl-, 3-F_3C; R′: Me, Et-, H-) were prepared and then described and reported as potent insecticides [53, 54].

3.1.7. Weed controlling agents

N-Aryl (C_{3-5}) alkane hydrazonoyl chlorides (R-C(Cl)=NNH-Ar; $R = C_nH_{n-1}$, $n = 3, 4, 5$) were first used as miticides and insecticides, against cotton ball weevil , herbicides and Mexican bean beetle housefly of crabgrass, yellow foxtail and wild oats [53, 55].

3.2. Utility of Hydrazonoyl Halides as Efficient electro-chemical sensors

Faisal et al., [56]has synthesized a novel hydrazonoyl bromide (HB) incorporating trifluoromethyl scaffold. He used the newly synthesized hydrazonoyl bromide in preparation of highly sensitive Cd^{2+} sensor with sensitivity approximately 51.12 μAμM−1cm^{-2}) and detection limit (~53.85±2.69 pM).[56]

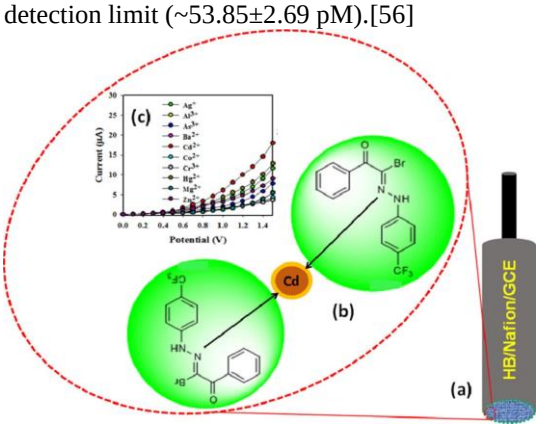
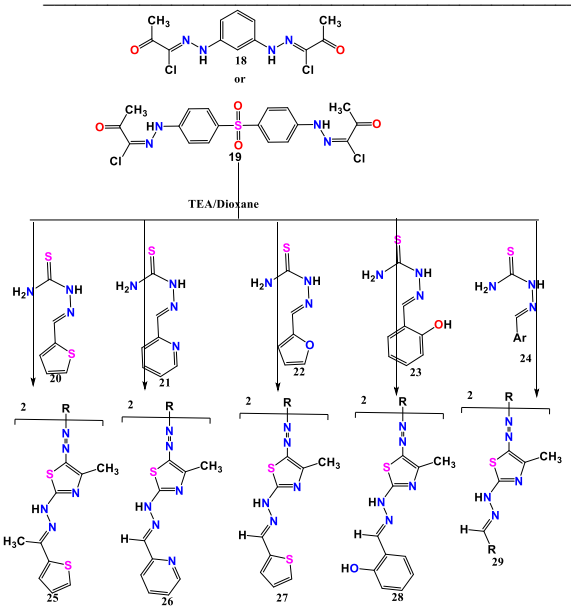


Figure 1: Utility of hydrazonoyl bromide (HB) incorporating trifluoromethyl scaffold as Efficient electro-chemical sensors, Copyright 2021. Reproduced with permission from Elsevier.

3.3. Utility of Hydrazonoyl Halides in synthesis of New Bioactive Heterocycles

3.3.1. Synthesis of Bis-thiazoles using bis-hydrazonoyl halides

In this regard, Sayed et al., [57]and coworkers have prepared a novel group of bis-thiazoles **25-29** by submitting a series of of bis hydrazonoyl halides **18** or **19** to react with various thiosemicarbazide derivatives **20-24**. The reaction was carried out in refluxing dioxane with the addition of catalytic amount of TEA at 105 ºC to give the corresponding desired bis-thiazoles-based molecules (**Scheme 12**).[57]



Scheme 12: synthesis of bis-thiazoles 25-29

3.3.2. Green Synthesis Novel Pyrimidotriazinoazepines utilizing hydrazonoyl chloride derivatives

Fariba et al.,[58] has developed novel derivatives of pyrimidotriazinoazepine (**36**) in excellent yield through one-pot multicomponent reactions of isatins (**30**), electron deficient acetylenic derivatives (**31**), α-haloketone derivatives (**32**), ammonium acetate (**33**), isocyanates (**34**) and hydrazonoyl chlorides (**35**). The reaction was performed at room temperature in aqueous medium. (**Figure 2**)

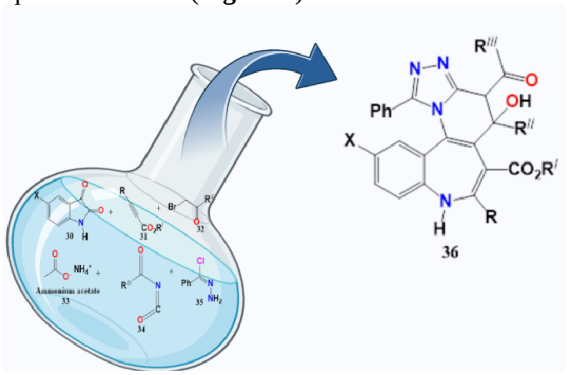
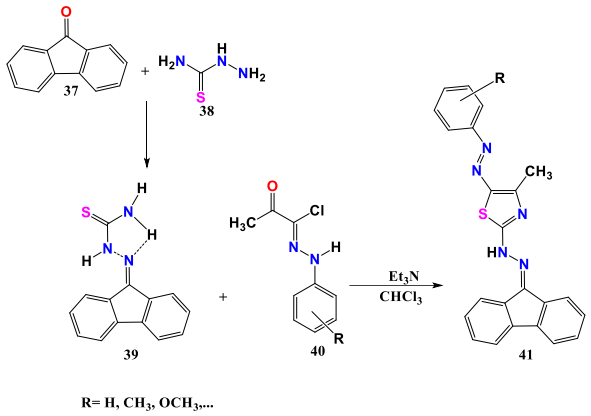


Figure 1: Diagram illustrated the synthetic procedures of pyrimidotriazinoazepine

3.3.3. Utility of Hydrazonoyl Halides in the synthesis of fluorene-based azo dyes containing thiazole scaffold

Nizar et al., [59] and coworkers have developed a series of novel eight fluorene/thiazole-based arylazo dyes (**41**) through the reaction of carbothioamide precursor (**39**) with selected derivatives of hydrazonoyl halides in chloroform in the presence of TEA (**40**). (**Scheme 13**)



Scheme 13: Synthesis of fluorene-based azo dyes containing thiazole scaffold **41**

3.3.4. Synthesis of thiazole based molecules as Covid-19 TMPRSS2 Enzyme Inhibitors

Rashdan et al., [60] has developed a novel series of thiazole based scaffolds and studied their efficacy as Covid-19 TMPRSS2 Enzyme Inhibitors via *in silico* study. The obtained results revealed that compound **42** (**Figure 3**) revealed promising binding affinity towards TMPRSS2 enzyme (**Figure 4**).

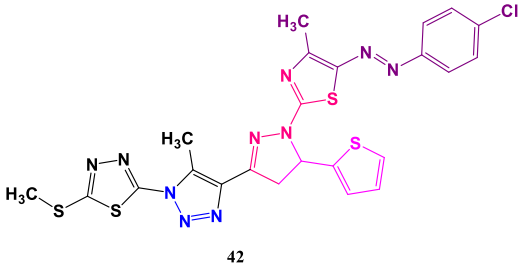


Figure 3: Chemical Structure of the thiazole based molecule **42**

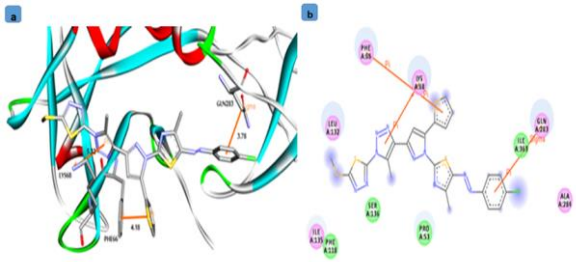


Figure 4: (**a**) (3D), and (**b**) (2D) representations of the binding interactions of the docked compounds **42** against TMPRSS2 (PDB ID: 1z8g)

3.3.5. Hydrazonoyl bromide precursors as DHFR inhibitors for the synthesis of bis-thiazolyl pyrazole derivatives

Seham et al., have synthesized a series of novel bis-thiazolyl pyrazole based molecules through the reaction of the appropriate of bis hydrazonoyl

bromides with selected active methylenes through one-pot reaction. They studied the antimicrobial potency of the newly developed derivatives. The obtained results revealed excellent antimicrobial potency toward the gram-positive strains, especially *S. aureus* (ATCC6538). They also studied the antibiofilm activity and the drug combinations against *MRSA*.[38]
(**Figure 5**)

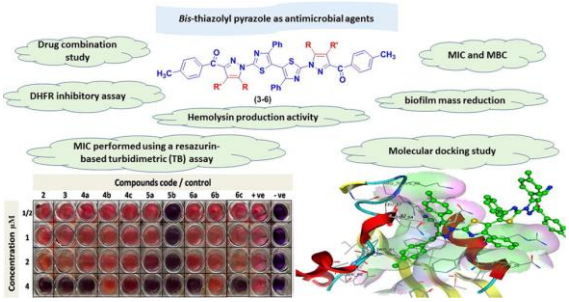
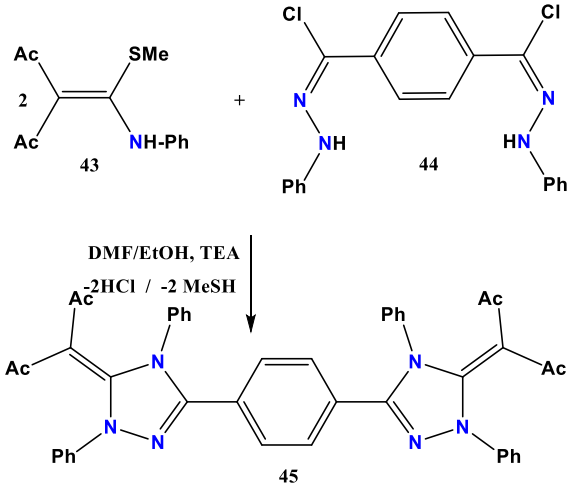


Figure 5: Synthesis of novel bis-thiazolyl pyrazole based molecules as potent antimicrobial agents, Copyright 2021. Reproduced with permission from Elsevier.[38]

3.3.6. Synthesis of 3,3′-bis-(1,2,4-triazole) derivatives utilizing bis-hydrazonoyl chlorides

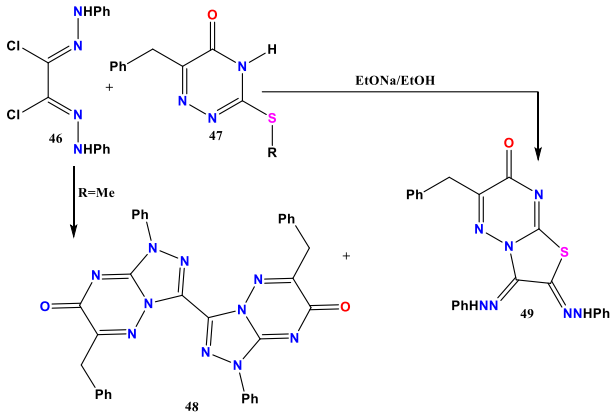
It was reported that the reaction of two mol equivalents ketene-N,S-acetal **43** with the appropriate of bis-hydrazonoyl chloride **44 in** DMF/EtOH under reflux in the presence of TEA give 3,3′-*bis*-(1,2,4-triazole) derivatives **45 (Scheme 14)[61]**



Scheme 14: Synthesis of 3,3′-*bis*-(1,2,4-triazole) derivatives **45**[61]

3.3.7. Utility of bis-hydrazonol halides in synthesis of novel polycyclic compounds

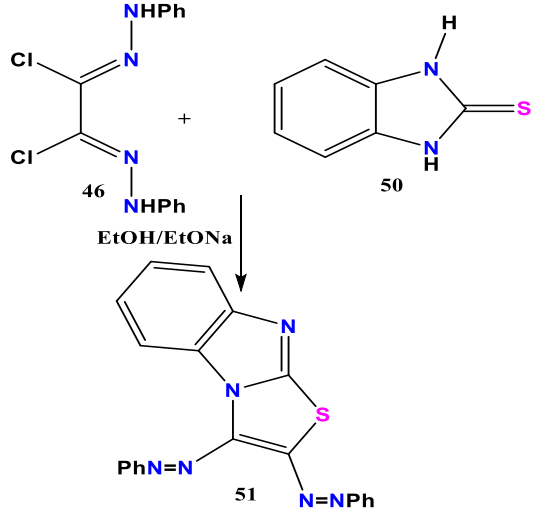
The reaction of the bis-hydrazonoyl chloride **46** with thioxo-1,2,4-triazinone derivative **47** in the presence of catalytic amount of sodium ethoxide in ethanol at room temperature afforded a mixture of the polycyclic compounds **48** (10%), **49** (72%). However, when the reaction was performed between the bis- hydrazonoyl chloride **46** and methyl thio derivative of compound **47** it afforded only **48** in excellent yield. (**Scheme 15**) [62]



Scheme 15: Synthesis of the polycyclic compounds **48** and **49**

3.3.8. Synthesis of 5,6-bis(phenylhydrazono)-2-phenyl-thiazolo[3,2-*a*]benzimidazole using bis-hydrazonoyl chloride derivatives

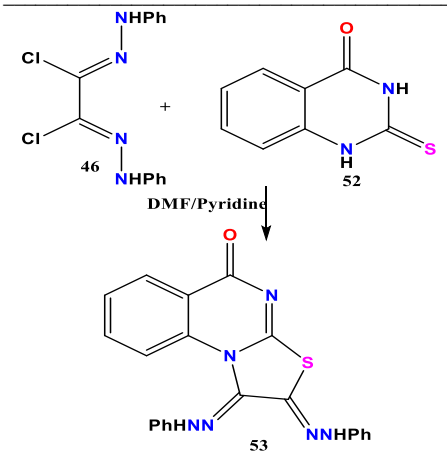
It was reported that by submitting imidazole-2-thione (**50**) to react with the selected bis-hydrazonoyl chloride derivative **46** at room temperature in ethanol in the presence of sodium ethoxide or under reflux using chloroform as a solvent in the presence of catalytic amount of TEA it gives the corresponding thiazolo-benzimidazole derivative (**51**)in good yield (**Scheme 16**) [47]



Scheme 15: Synthesis of 5,6-bis(phenylazono)-2-phenyl-thiazolo[3,2-*a*]benzimidazole (**51**)

3.3.9. Synthesis of bis-(phenylhydrazono)-thiazoloquinazolines

Shawali et al., [63] has reported the synthesis of novel bis-(phenylhydrazono)-thiazoloquinazoline derivative **53** via the regioselective reaction of the bis hydrazonoyl halide **46** with 2-thioxoquinazolin-4(1*H*)-one **52** in 1:2 molar ratios under reflux in DMF/pyridine. (**Scheme 16**)



Scheme 16: Synthesis of bis-(phenylhydrazono)-thiazoloquinazolines

4. Conclusion and Future Work

The present review clarified those hydrazonoyl halides are a hot topic of pharmaceutical and biomedical research owing to their versatile chemical reactions. They are easily to synthesized via wide range of different starting materials which can be utilized for the generation of new heterocyclic molecules. In addition, hydrazonoyl halides have a broad spectrum of biological and pharmaceutical applications. It is hoped that this review will be fruitful favorable base for continuing improvements and investigations of their chemistry.

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