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HIGHLIGTHS IN 1,2,3-DITHIAZOLE CHEMISTRY

Hélène Laborie, Hervé Rouillard, Emmanuel Deau, Philippe Pineau, Lisianne Domon, Jean-René Chérouvrier, Valérie Thiéry*

University of La Rochelle, UMR CNRS 6250 LIENSs, Bât. Curie, Avenue Michel Crépeau, 17042 La Rochelle, France

*Corresponding author: vthiery@univ-lr.fr

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Abstract: Among the five-membered heterocycles containing nitrogen and sulphur atoms, 1,2,3-dithiazoles are important compounds due to their unusual physical properties, biological activity and versatile chemistry. The present review presents data on Appel's salt and on the syntheses and reactions of imino-1,2,3-dithiazoles obtained over the recent 10 years.

Keywords: *1,2,3-dithiazoles, Appel's salt, dithiazolium salts*

In memory of Professor Charles W. Rees from Imperial College of London

SYNTHESIS OF 1,2,3-DITHIAZOLIUM SALTS

In 1985, Appel and co-workers first described some of the chemistry of 4,5-dichloro-1,2,3-dithiazolium chloride **1** also called Appel's salt [1]. This salt, a pale greenish solide is readily prepared from chloroacetonitrile and sulfur monochloride in presence of Adogen [2] (Figure 1).

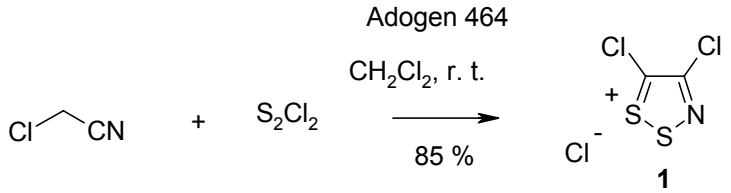


Figure 1. *Synthesis of 4,5-dichloro-1,2,3-dithiazolium chloride*

Recently, Koutentis extended this salt-forming reaction to various acetonitrile derivatives with S_2Cl_2 at room temperature and reported the preparation of a rank of 5-substituted-4-chloro-1,2,3-dithiazolium salts in good yields (Figure 2) [3].

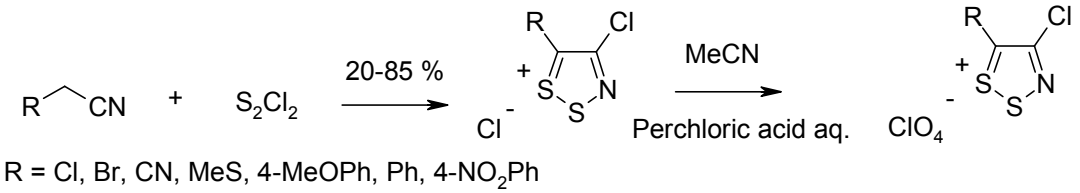


Figure 2. *Synthesis of 5-substituted-4-chloro-1,2,3-dithiazolium chloride*

A possible extensively studied 4,5-dichloro-1,2,3-dithiazolium chloride analogues was also found in the synthesis 4-substituted-5-chloro-1,2,3-dithiazolium chlorides by reaction of acetophenone oxime and its 4-nitro derivative with S_2Cl_2 (Figure 3) [4].

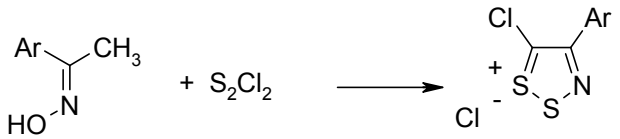


Figure 3. *Synthesis of 5-substituted-4-chloro-1,2,3-dithiazolium chloride*

Reactivity of Appel's salt 1

1,2,3-Dithiazoles have attracted much attention amongst five membered sulfur-nitrogen heterocycles because of their interesting physical and biological properties and versatile chemistry that has been reviewed [5-7]. Appel showed that the reactive 5-chlorine atom of Appel's salt could be displaced by a variety of nucleophiles (Figure 4) [1].

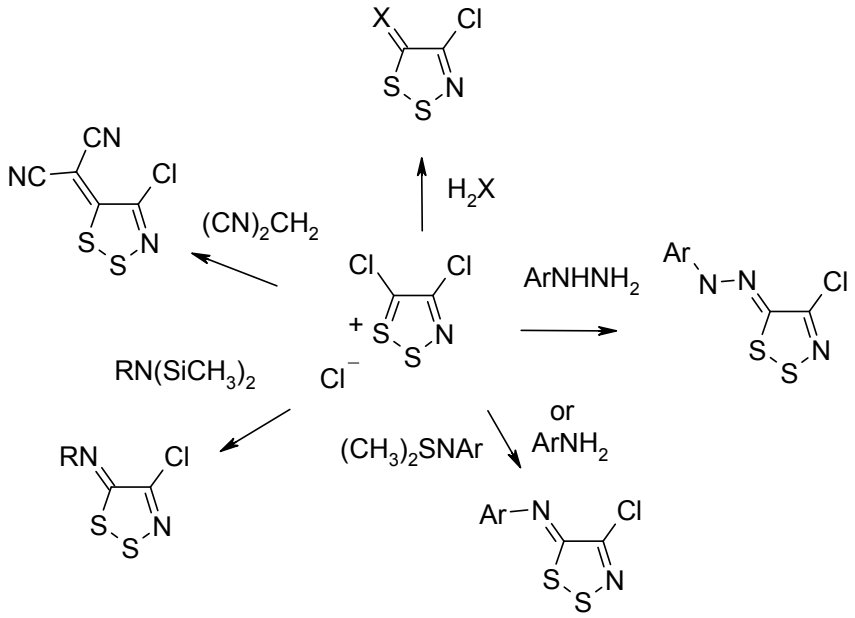


Figure 4. *Reactions of Appel's salt with N-nucleophiles*

Early chemistry was devoted to reactions with arylamines, phenol and active methylene compounds [8-15], and was widely developed by Rees [8], Kim [14-15] and more recently by Koutentis [16-19]. Koutentis showed that Appel's salt reacts in wet solvents (DCM, THF or MeCN) to give after degradation elemental sulphur, dithiazole-5-thione, dithiazol-5-one and thiazol-5-one (Figure 5) [16]. The use of catalytic amounts of DMSO (1 mol%) in MeCN in the presence of water (1 equiv) transforms Appel's salt into 4-chloro-1,2,3-dithiazol-5*H*-one in near quantitative yields [17].

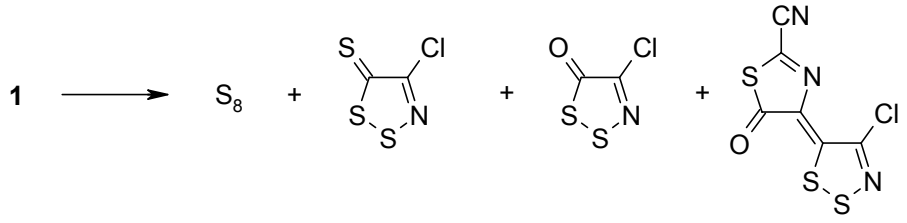


Figure 5. *Reaction of Appel's salt 1 in various solvents (DCM, THF, MeCN)*

Appel's salt reacts with dimethylsulfonium dicyanomethylide to afford in modest yield (4-chloro-1,2,3-dithiazolylidene)malonitrile besides a new methylthioacrylonitrile byproduct (Figure 6) [18-19].

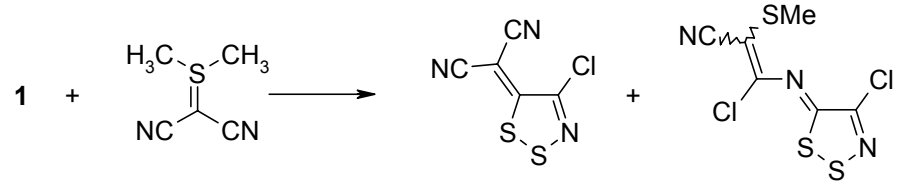


Figure 6. *Reaction of Appel's salt 1 with dimethylsulfonium*

N-ARYLIMINO-1,2,3-DITHIAZOLES

Nitrogen-containing heterocycles with sulfur atom are an important class of compounds in medicinal chemistry. Neutral 1,2,3-dithiazoles show interesting antibacterial, antifungal and herbicidal activities. Since their first appearance in 1977, much attention has been focused on 5-aryl-4-chloro-5*H*-1,2,3-dithiazoles owing to their potential synthetic utility and biological importance against some fungi, grasses and broad-leaved weeds [20-21]. Owing to their growing use in compounds of therapeutic importance (antibacterial, anticancer drugs), the synthesis of *N*-heteroimino-1,2,3-dithiazole derivatives has been actively pursued in the last past decade [22-26].
In order to enhance potential antimicrobial activity of the dithiazole derivatives, Besson and coworkers varied the structures of the aryl groups with more complex aromatic moiety starting from substituted anilines, quinoline and naphthalene derivatives and prepared new series of *N*-arylimino-1,2,3-dithiazoles (Figure 7) [22-25]. These compounds mainly exert antibacterial activity against gram-positive bacteria.

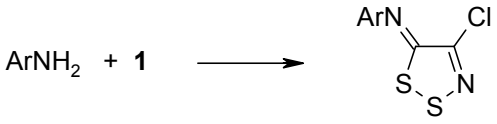


Figure 7. *N-Aryliminodithiazoles from aminoheterocycles*

More recently, Thiéry and Rakitin reported the synthesis and biological evaluation of rare 4-substituted-5-phenylimino, 5-thieno- and 5-oxo-1,2,3-dithiazoles [27]. Dithiazoles were selectively obtained in moderate to high yields (25-73%) via a one pot reaction from various ethanoneoximes with sulfur monochloride, pyridine in acetonitrile followed by treatment by corresponding nucleophiles (aniline, thioacetamide and formic acid) (Figure 8).

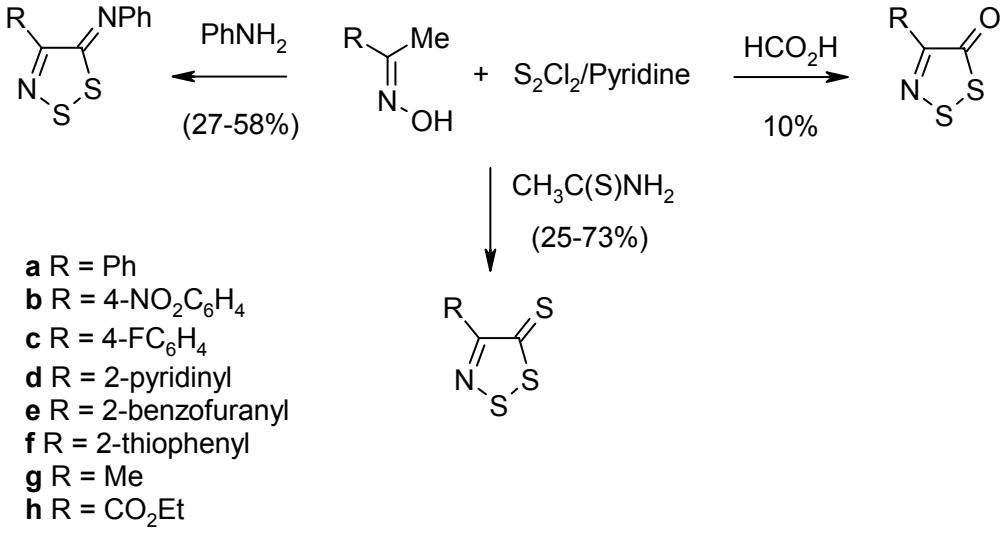


Figure 8. *5-N-Aryl-4-substituted-1,2,3-iminodithiazoles and 5-thieno- and 5-oxo-1,2,3-dithiazoles derivatives*

All the synthesized compounds were screened for their antibacterial (against bacteria *Escherichia coli*, *Salmonella enterica serovar Typhimurium*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Enterococcus faecalis*, *Bacillus cereus* and *Listeria inocua)*, antifungal (against pathogenic strains *Candida albicans*, *Candida glabrata*, *Candida tropicalis* and *Issatchenkia orientalis)* and antitumor (on human cell lines MCF-7 and MDA-MB-231) activities. 4-(2-Pyridinyl)-5*H*-1,2,3-dithiazole-5-thione and 4-ethylcarboxyl-5*H*-1,2,3-dithiazole-5-thione that are active against Gram positive bacteria are significantly active against fungi. 4-(2-Benzofuranyl)-5-phenylimino-5*H*-1,2,3-dithiazole exerts antiproliferative activity. In all cases, the 1,2,3-dithiazole ring acts as a powerful inhibitor of several enzymes structurally related to serine proteases.

Reactivity of 4-chloro-5-heteroimine-5*H*-1,2,3-dithiazoles

Primary aromatic amines are readily converted into stable imino-1,2,3-dithiazoles. *N*-Arylimino-1,2,3-dithiazoles are highly versatile intermediates in heterocyclic chemistry, undergoing a variety of reactions initiated by nucleophilic attack at different sites on the dithiazole ring. Some of these reactions transform the dithiazole ring only, whilst other involve cyclisation onto the adjacent ring (Figure 9).

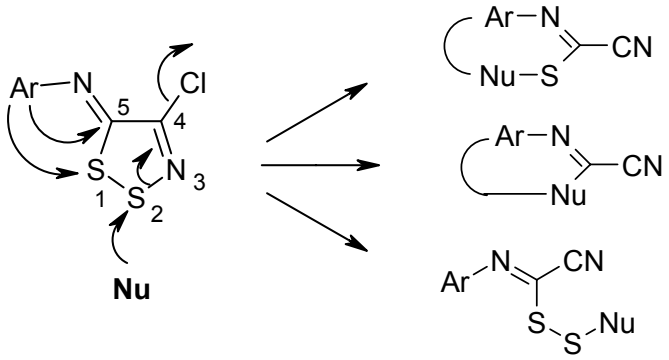


Figure 9. *Chemical transformations of N-arylimino-1,2,3-dithiazoles*

Dithiazole ring opening

Besson and Thiéry previously showed that reduction of the imines in the presence of various hydrides afforded cyanothioformanilides, isothiocyanates or the rearranged *N*-aryldithiooxamides (Figure 10) [28-29].
Recently Koutentis discovered a new transformation of 2-(4-chloro-5*H*-1,2,3-dithiazolylideneamino)benzonitriles into 3-amino-indole-2-carbonitriles in moderate yields using either free triphenylphosphine or polymer bound triphenylphosphine (Figure 11) [30].
Reaction of the same 1,2,3-dithiazolimines with an excess of DBU give the corresponding 2-cyano cyanothioformanilides in near quantitative yields (Figure 12) [31].

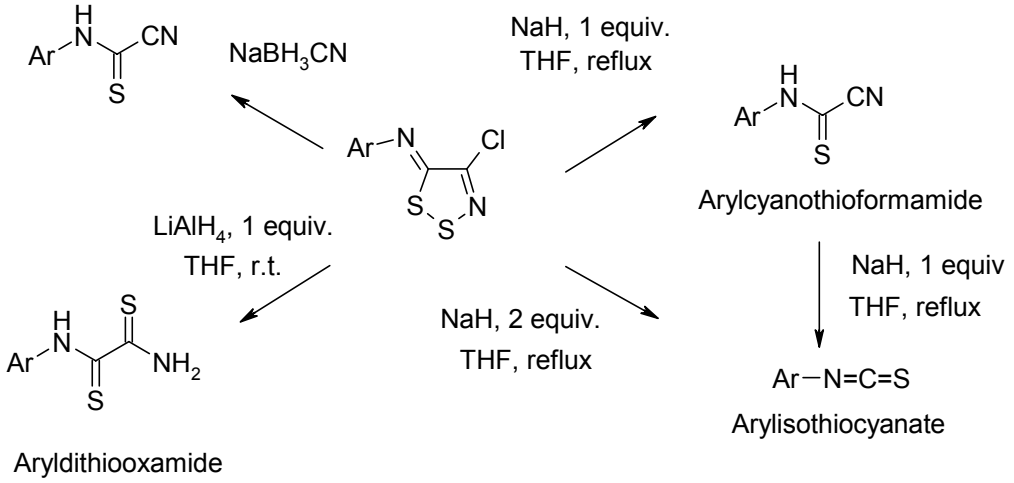


Figure 10. *Ring opening of N-arylimino-1,2,3-dithiazoles with hydrides*

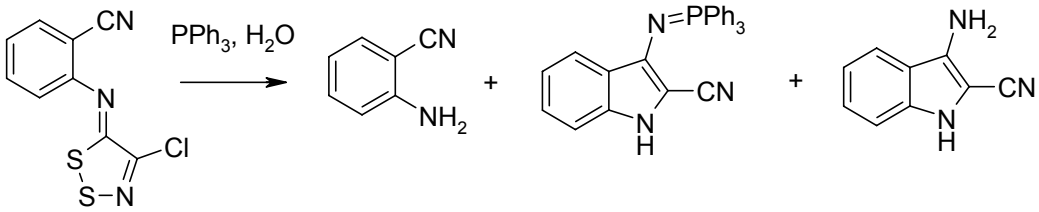


Figure 11. *Formation of 3-amino-2-carbonitrile from 2-(4-chloro-5H-1,2,3-dithiazolylyideneamino)benzonitrile*

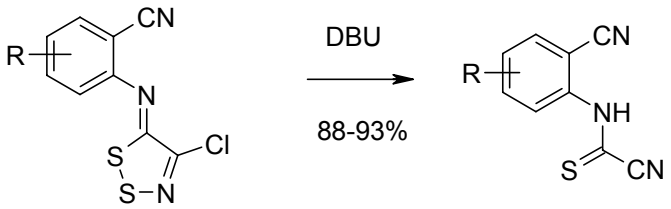


Figure 12. *Synthesis of 2-cyano-cyanothioformanilides*

N-Arylimino-1,2,3-dithiazoles: versatile intermediates in heterocyclic synthesis

Exploring original approaches for the synthesis of therapeutic agents having a quinazoline part and inspired by previous works of Kim [14], Pereira and coworkers confirmed that primary alkyldiamines may react easily with the dithiazoloimine methylanthranilates to afford quinazolines, which are very interesting starting materials for access to novel 2,3-condensed quinazolin-4-ones (Figure 13) [32-35].

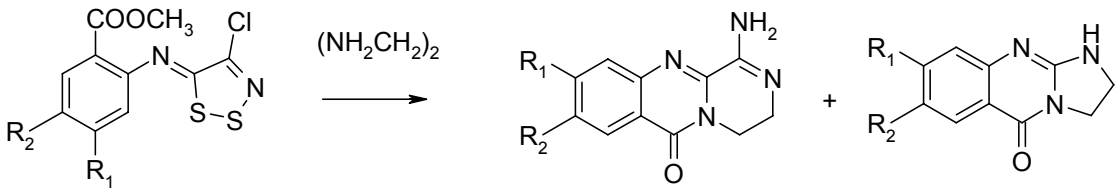


Figure 13. *Synthesis of imino-2,3-dihydro-1H-pyrazino[2,1-b]quinazolin-5-ones*

Extending the potential applications of Appel salt, Pereira investigates also the synthesis of novel 2,3-condensed thieno[2,3-*d*]pyrimidinones by condensation of aromatic or semi-aromatic diamines on the starting thieno 3-imino1,2,3-dithiazoles [36]. Contrary this previously published work, Laborie and Rouillard [37] showed that the methyl *N*-dithiazoloiminethiophene-3-caboxylate counterparts could be obtained in modest to good yields and could be used as new intermediate for the preparation of various new heterocyclic rings (Figure 14).

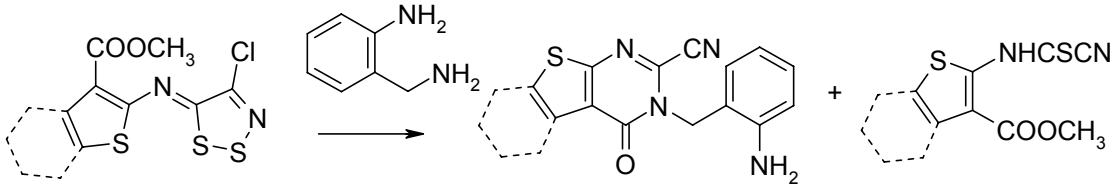


Figure 14. *Synthesis of thienopyrimidinones*

Thermolysis

The thiazole ring, present in various natural and synthetic products, has generated interest of many groups on account of its useful biological properties.
During the last ten years, our interest in biologically active compounds as potential antitumor agents focused our studies on the synthesis of new derivatives in which the thiazole ring might be fused to polyheterocyclic systems. It has been shown that 5-(*N*-arylimino)-4-chloro-5*H*-1,2,3-dithiazoles, which are stable crystalline solids readily prepared from primary aromatic amines and Appel salt, cyclized by vigorous heating to give sulfur, hydrogen chloride and 2-cyanobenzothiazoles (Figure 15) [1, 8, 38].

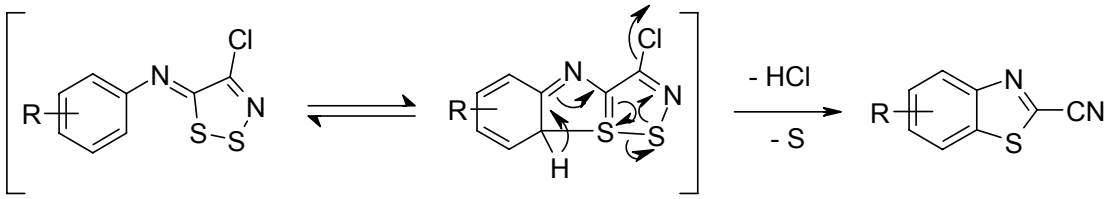


Figure 15. *Synthesis of 2-cyanobenzothiazoles from N-aryliminodithiazoles*

Thiéry has shown that thermolysis of *N*-(8-quinolinyl)iminodithiazoles led to an unusual type of thermal rearrangement to give the new imidazo[4,5,1-*ij*]quinolines-4-thiones (Figure 16) [39].
The thione is delivered intramolecularly. The quinoline nitrogen participates as a neighbouring nucleophile to give the imidazoquinoline which can collapse to a tetracyclic species. Elimination of HCl and loss of one sulphur atom from the intermediate 7-membered ring give the imidazoquinolithiones (Figure 17) [40].
Various methodologies under conventional conditions or microwave irradiation where also developed in Besson's group: heating the iminodithiazole in sealed vials in the presence of non polar solvent or under microwave irradiation in the presence of polar solvent such as *N*-methylpyrrolidin-2-one; direct exposition of the imines (neat in glass vials with a screw cap lid) with carbon graphite [41, 42].

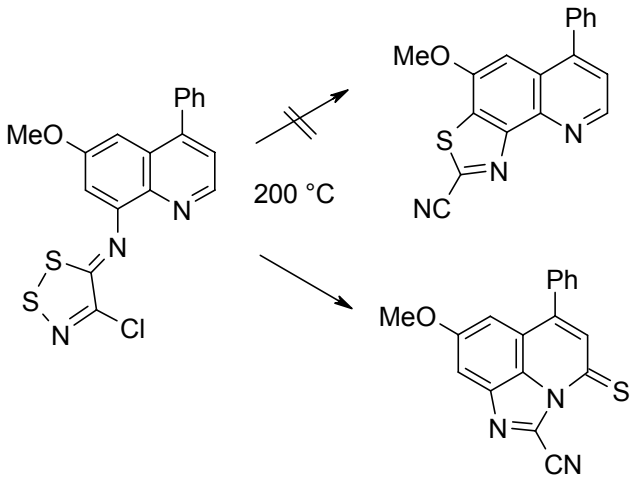


Figure 16. *Thermolysis of N-(8-quinolinyl)iminodithiazoles*

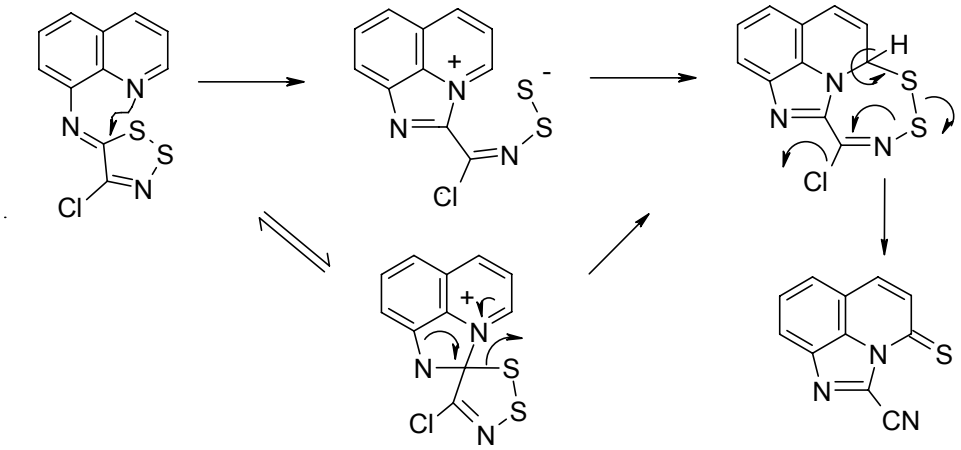


Figure 17. *Imidazoquinolinethiones from quinolines: a new molecular rearrangement*

In order to obtain regioselectively the linear or angular thiazolo isomers, Guillard and coworkers described a mild procedure which consists in heating *ortho* bromoimines in the presence of cuprous iodide in pyridine at reflux (Figure 18) [43].

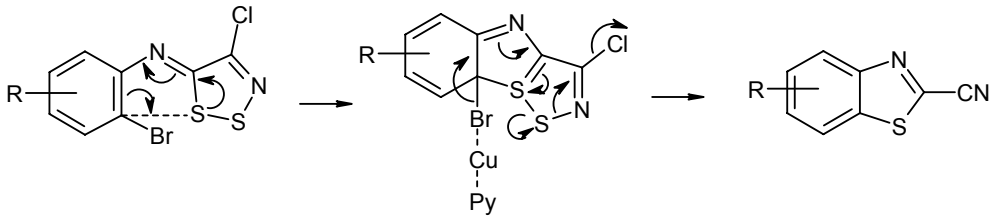


Figure 18. *Synthesis of benzothiazoles from orthobromoimines*

In this context, the regiocontrolled synthesis of substituted thiazolocarbazoles and bioisosteres mainly related to marine or terrestrial alkaloids (e.g. dercitine, kuanoniamine and ellipiticine) (Figure 19) [44-48] and thiazoloquinazolinones structurally closed to Roscovitine (Figure 20) [49-51] was reported.

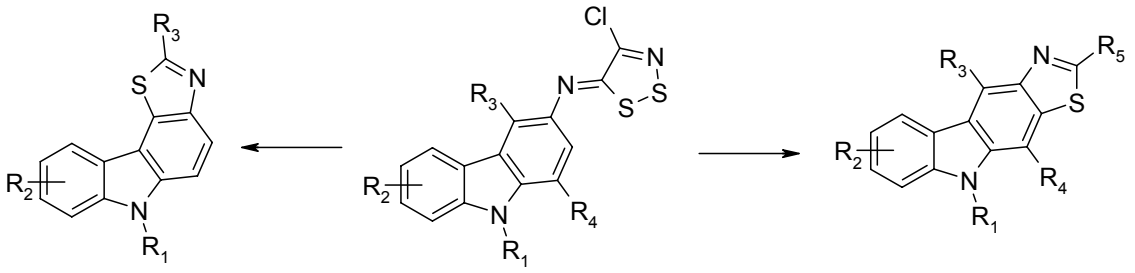
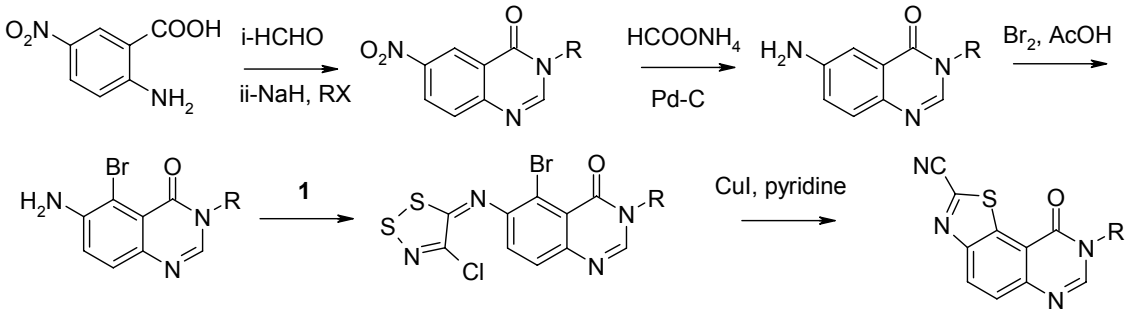


Figure 19. *Synthesis of thiazolocarbazoles*



R = Me, Et, Pr, iPr, $(CH_3)_2CHCH_2CH_2$, Bn, 4-MeOBn, $(CH_3)_2NCH_2CH_2$.

Figure 20. *Microwave-assisted synthesis of thiazoloquinazolinones*

According to the same strategy, recently Beauchard reported the synthesis of a novel angular thiazolobenzotriazole (Figure 21), a key intermediate for the synthesis of new thiazoloindolo[3,2-*c*]quinoline skeleton (Figure 22) [52-53].

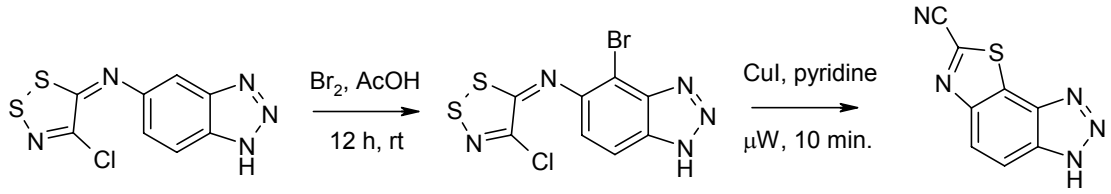


Figure 21. *Cyclization of (1H-benzotriazol-5-yl)-(4-chloro-[1,2,3]dithiazol-5-yliden)amine*

Reaction was performed via the Graebe-Ullmann thermal ring transformation from original thiazolobenzotriazole, besides unexpected rare 10-*N*-substituted-7*H*-4,7-diaza-benzo[*de*]anthracene (Figure 22) [52].

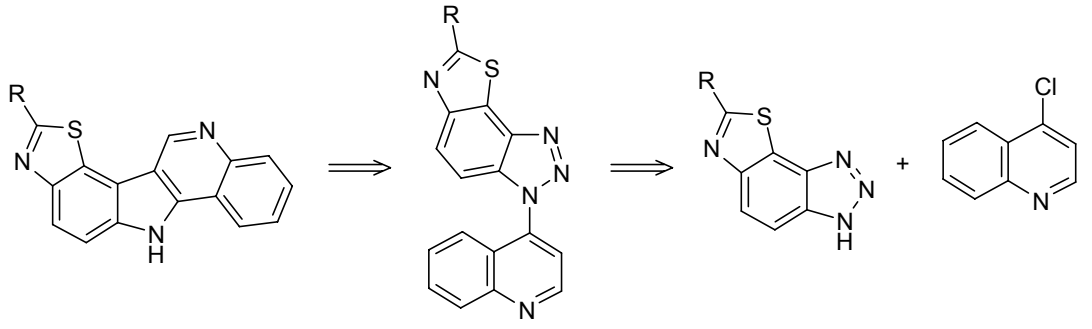


Figure 22. *Retrosynthetic pathway to thiazoloindoloquinoline derivative*

The work described in this review represents further examples of the importance of 1,2,3-dithiazole skeleton in chemistry and medicinal chemistry, utility of Appel's salt in the conception of novel heterocyclic rings to access to original bioactive compounds.

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