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STUDIES ON THIAZOLE

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Introduction: Thiazoles are one of the most intensively investigated classes of aromatic five-membered heterocycles. It was first described by Hantzsch and Weber in 1887. This five membered ring system containing sulfur and nitrogen heteroatoms at positions-1 and -3, respectively is involved in many of the natural products.

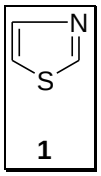

Figure 1 Structure of thiazole

For example, the thiazolium ring present in vitamin B1 (2) serves as an electron sink, and its coenzyme form is important for the decarboxylation of α-keto acids. Thiazole and its derivatives are very useful compounds in various fields of chemistry including medicine and agriculture. In addition, thiazoles are also synthetic intermediates and common substructures in numerous biologically active compounds such as various derivatives of penicillins (3) and antibacterial thiazoles. Reduced thiazoles serve in the study of polypeptides and proteins and occur as structural units in compounds of biological importance.

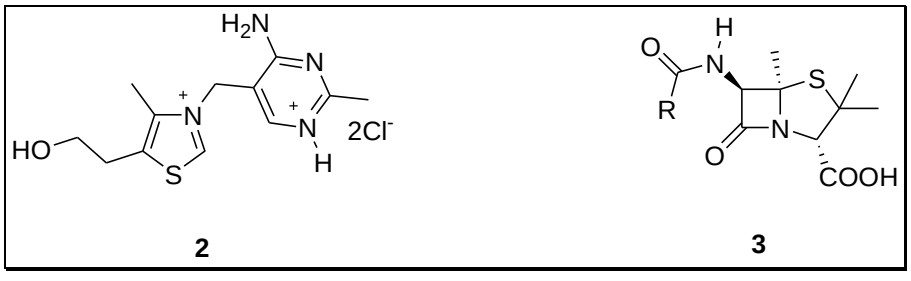

Figure 2 Structure of Thiamine and Penicillin G

The properties of thiazole are similar to those of oxazole and the nitrogen atom with unshared pair of electron is basic in nature. Among the different aromatic heterocycles, thiazoles

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occupy a prominent position in the drug discovery process and this ring structure is found in several marketed drugs which are given below with their pharmaceutical activity. It can also be used in a scaffold hopping strategy or as an amide isostere during the course of probing structure activity relationships for lead optimization. As a result, thiazoles are frequently included in the design or are used as a core structure for the synthesis of chemical libraries. Thus the thiazole nucleus has been much studied in the field of organic and medicinal chemistry.

Among the different aromatic heterocycles, thiazoles occupy a prominent position in the drug discovery process[13] and this ring structure is found in several marketed drugs such as meloxicam (anti-inflammatory) (**4**), sulfathiazole (antibiotic) (**5**), tiazofurin (anticancer) (**6**), abafungin (antifungal) (**7**) etc. which are given below (**figure 3)** with their pharmaceutical activity. It can also be used in a scaffold hopping strategy or as an amide isostere during the course of probing structure activity relationships for lead optimization. As a result, thiazoles are frequently included in the design or are used as a core structure for the synthesis of chemical libraries. Thus, the thiazole nucleus has been much studied in the field of organic and medicinal chemistry.

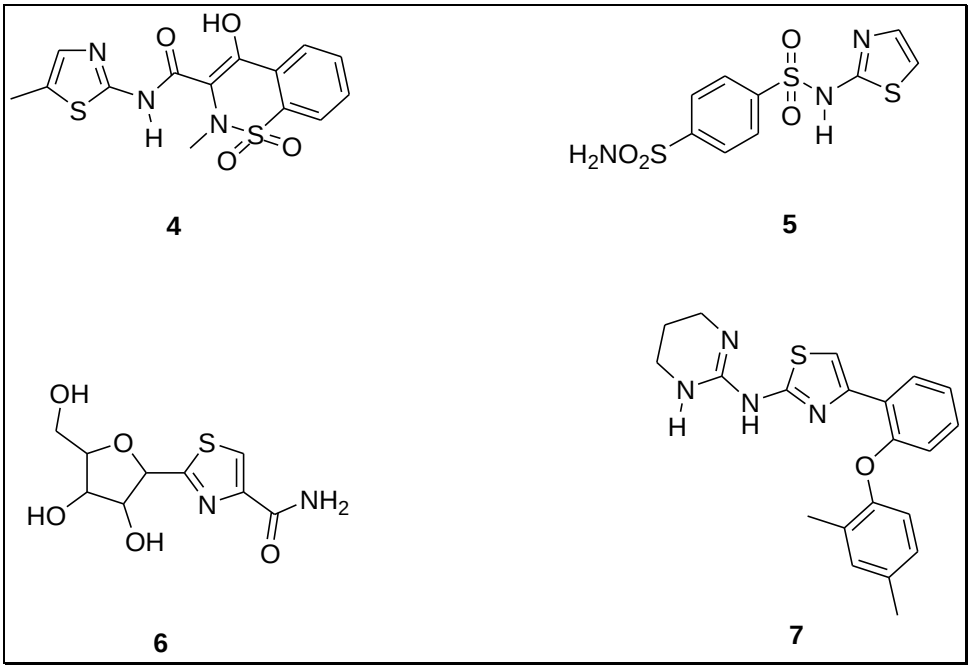

Figure 3 Clinically used thiazoles.

It is evident from the above literature that thiazoles are associated with various biological activities. The synthesis of thiazoles can be effected by using large number of methods.

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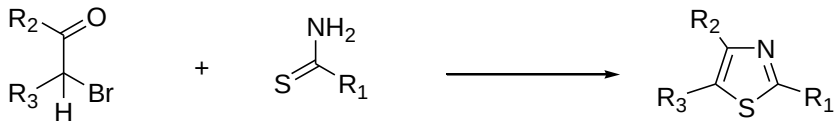
MOST COMMON SYNTHETIC PROCEDURE

Synthesis from α-halocarbonyl compounds (Hantzsch's synthesis):

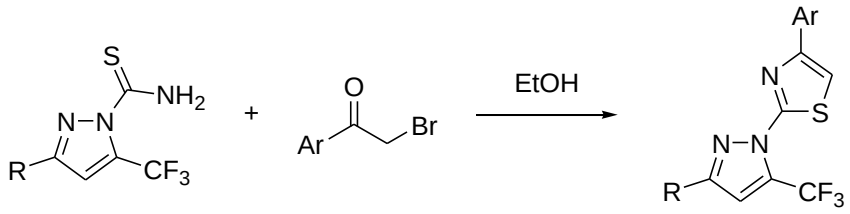
First described in 1887 by Hantzsch, the cyclization of α-halo carbonyl compounds by a great variety of reactants bearing the N-C-S fragment of the ring is still the most widely used method of synthesis of thiazoles **(Scheme 1)**.



8 **9** **10**

Scheme 1

Later on, aggarwal *et al* have reported reaction of 3-trifluoromethylpyrazol-1-thiocarboxamides **11**, regioselectively obtained by the condensation of trifluoromethyl-β-diketones with thiosemicarbazide under neutral and acidic conditions, with phenacyl bromides **12** to gave 4-aryl-(3-trifluoromethyl-pyrazol-1-yl)thiazoles **13** (**Scheme 2**).



11 **12** **13**

Scheme 2

El Hady *et al* have demonstrated the synthesis of thiazoles *via* cyclization of *p*-methyl acetophenone thiosemicarbazone **(15)** with *p*-methylphenacyl bromide and ethyl chloroacetate in presence of fused sodium acetate (**Scheme 3**).

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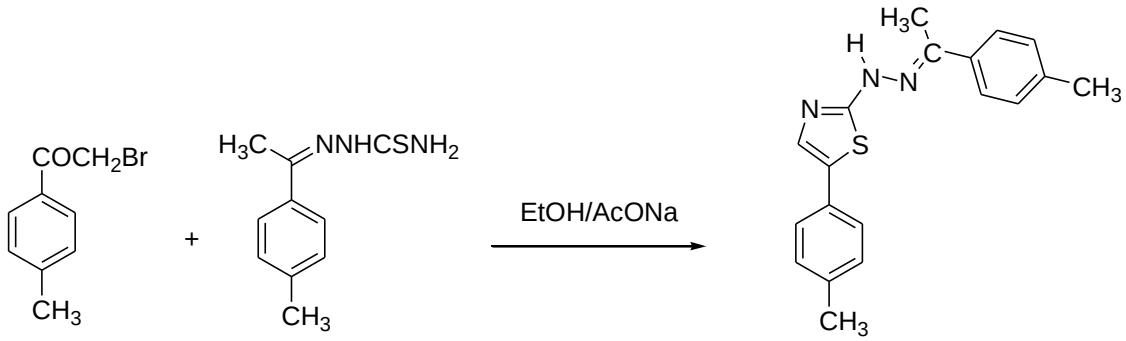
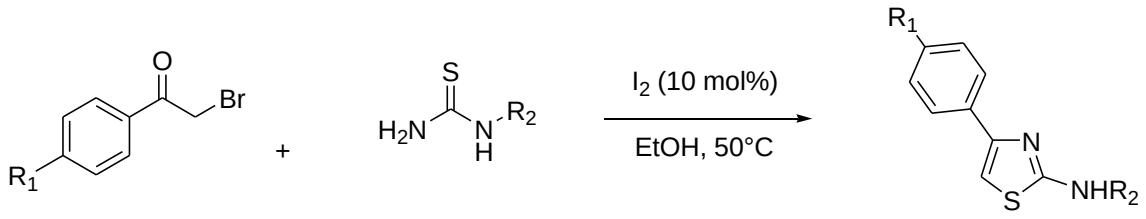


14 **15** **16**

Scheme 3

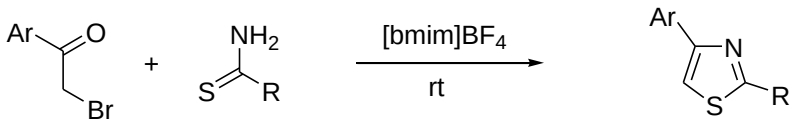
In another study, synthesis of 2-aminothiazoles (**19**) has been accomplished by using molecular iodine catalyzed condensation of α-bromoketones (**17**) with thioureas (**18**). The advantage of this method is that pure products are formed very rapidly under mild conditions (**Scheme 4).**



17 **18** **19**

Scheme 4

A highly efficient and rapid synthesis of 2-amino/methyl-4-arylthiazoles (**20**) from α-bromoketones (**12**) and thioureas/thioacetamide was described by Potewar *et al.* using room temperature ionic liquid (IL) at ambient conditions. This protocol was utilized for a commercially feasible synthesis of an anti-inflammatory agent, Fanetizole (**Scheme 5**).



12 **20**

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