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Synthesis of 2-aminothiazole derivatives: A Short Review

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Introduction:

There are many chemistry applications for thiazole and its derivatives, including in agriculture and medicine. For instance, B1 vitamins include in thiazolium molecule that functions like the electron absorbent, whose coenzyme form is crucial for the decarboxylation of the keto acids.[1] This heterocyclic system offers a wide range of applications in the creation of medications for the management of inflammatory conditions,[2] hypertension,[3] bacterial[4] infections, including HIV infections.[5] In addition to being a novel class of adenosine receptor antagonists,[6]aminothiazoles are known to be ligands of oestrogen receptors.[7] Other analogues are employed as fungicides, schistosomicidal and *Xanthomonasto vivo* growth inhibitors, herbicide ingredients, and anthelmintic medications.[8] An anti-inflammatory drug is fentiazac, a 2-aminothiazole derivative. Thiazoles are also prevalent substructures in many biologically active chemicals and synthetic intermediates. As a result, the thiazole nucleus has received considerable attention in the fields of chemical and medical chemistry.

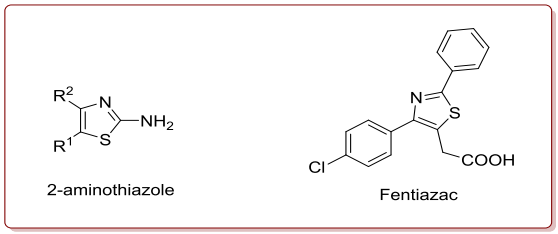


Figure 1. Structures of 2-aminothiazoles

A widely occurring structural component in pharmacological compounds is 2-aminothiazole. In the *Journal of Medicinal Chemistry*, more than 100 publications describing compounds containing 2-aminothiazoles are published in the past ten years. These studies show action for a wide variety of biological targets. There is strong evidence to support the idea that libraries of 2-aminothiazoles might provide physiologically active compounds. A reliable and well-known method for producing 2-aminothiazoles in high yields from easily available substrates is the Hantzsch synthesis of 2-aminothiazoles from haloketones and thioureas, which was originally described in 1887.[9]

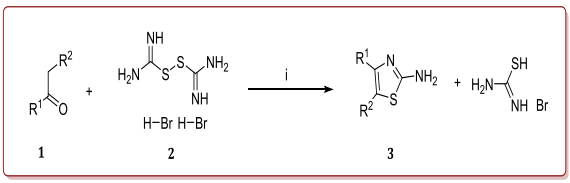
Previous Work:

Various methods for synthesis have been reported in the literature due to the significance of 2-aminothiazoles and their biological properties. Some of the most important techniques have been described in this section.

L. C. King et al. approach (1947)[10]

As reported by L. C. King et al., formamidine disulfide dihydrobromide **2** and ketone **1** were combined to create 2-aminothiazoles **3**. Ketone 1 and formamidine disulfide dihydrobromide **2** were added to a reaction mixture, which was heated overnight in a steam bath to produce 2-aminothiazole **3**. Thiourea and bromine were

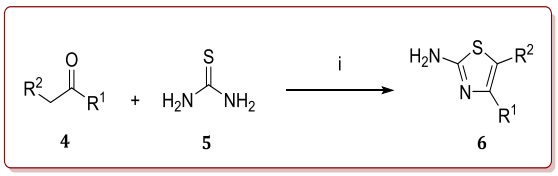
first used for producing formamidine disulfide dihydrobromide.



Scheme 1.Reaction conditions: (i) steam heated overnight at 19-48%.

L. Carroll King and his team's method (1950)[11]

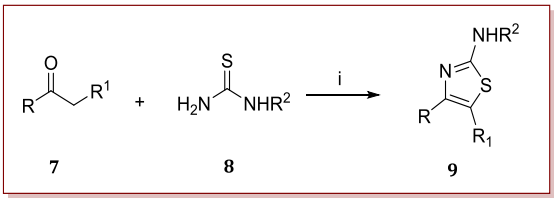
As reported by L. Carroll King et al., A combination with ketone **4** (1 eq.) and thiourea **5** (2 equiv), and iodine (1 equiv) produced 2-aminothiazoles **6**. In order to produce 2-aminothiazole derivatives, the reaction mixture contains the involved materials were heated overnight on a steam bath, extracted using ether to remove the beginning material, and then a by-product it was dissolved in hot water, then filtered to make basic.



Scheme 2. Reaction conditions: (i) Iodine (I_2),100°C (steambath), overnight, 18-97%.

H. K. Pujari et al. method (1986)[12]

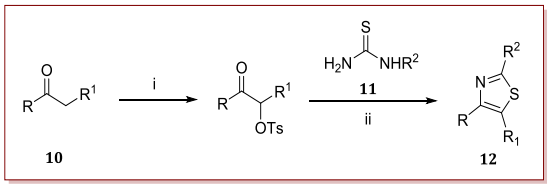
Applying N-bromosuccinimide (NBS), a catalytic quantity for benzoyl peroxide in the anhydrous form benzene at reflux conditions for a total of 6 hours on a steam bath, Pujari, H.K., and othersdecribed the synthesis is 2-aminothiazoles **9**. To get 2- aminothiazole, the hydrobromide salt that is produced was neutralised with potassium carbonate.



Scheme 3. Reaction conditions: (i) *N*-bromosuccinimide, benzoyl peroxide, and anhydrousbenzene, reflux for 6 h, 56-90%.

Ram P. Kapoor et al. method (1993)[13]

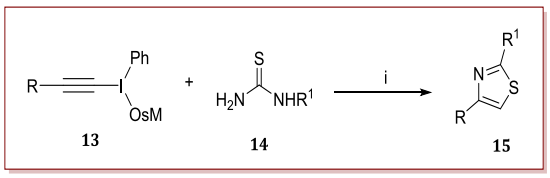
Ram P. Kapoor and colleagues described the formation for 2-substituted thiazoles **12** with reacting an enolisable ketone **10** using thallium (III) *p*-tolylsulfonate and a solvent in acetonitrile that is refluxing, following the use of thiourea or thioamide **11.** To get 2-substituted thiazoles, a previously produced salt was turned basic.



Scheme 4. Reaction conditions: (i) Thallanium (III) *p*-tolylsulfonate (TTS), MeCN reflux 20-30min; (ii) MeCN, reflux, 1-2h, K_2CO_3, 70-86%.

Peter Wipf et al. approach (1996)[14]

As reported by Peter Wipf et al., 2-substituted thiazoles**15** were produced by reacting mesylate of alkynyl(phenyl)iodonium**13** andthioamide**14** in a solvent like Et_2O, EtOAc, or MeOH at 0°C for 3 hours.

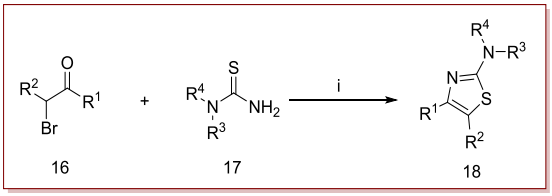


Scheme 5. Reaction conditions: (i)MeOH or Et_2O, carbonate or Et_3N, 3 h, 0°C, 32-64%.

Stephen P. Watson et al. method (1996)[15]

In 1996, Stephen P. Watson and coworkers reported the solution phase

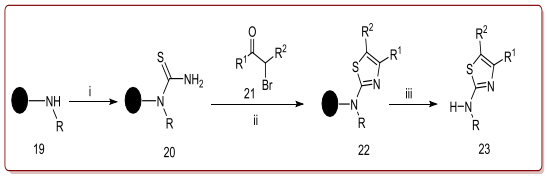
preparation process they used to synthesize 2-aminothiazoles **18** by reacting α-bromo ketones **16** andthiourea**17**were combined in DMF into 75 °C for 5 hours. A series of 2-aminothiazoles was produced in this manner.



Scheme 6. Reaction conditions :(i) DMF at 75°C for 5h, purity 44-98%.

John A. Flygare et al. method (1998)[16]

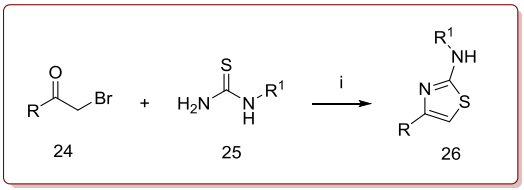
As reported by John A. Flygare and otherssynthesised 2-aminothiazole **23** began with resinboundamine, primary or secondary 19. In the beginning, **19** interacted using9-Fluorenylmethoxycarbonyl isothiocyanate (Fmoc-NCS) in produce thiourea that has been protected by Fmoc subsequent deprotection of Fmoc-group during simple circumstances produced purethiourea **20**. Thiazoles **23** have been produced by reacting resin-attached thiourea **20** and a solution of dioxane containing α-bromothe ketone group **21**.



Scheme 7. Reaction conditions: (i) fluorenylmethyloxycarbonylisothiocyanate (Fmoc-NCS), DCM, rt, 30 minutes; 20% piperidine in methanol, overnight; (ii) dioxane, rt ; (iii) 95% TFA, 5% H_2O, 65-77%

Simon S. W. Leung et al. approach (2000)[17]

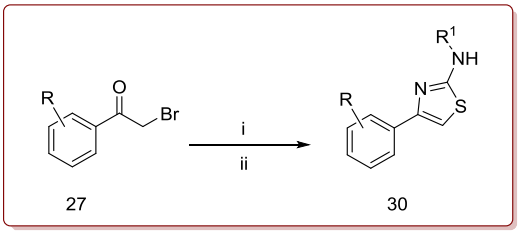
As reported by Simon S. W. Leung and coworkers, 2-aminothiazoles **26** were produced on heating a reaction mixture including in dry acetone at 57 °C, combine α-bromo ketone **24** with thiourea **25** for four hours.



Scheme 8. Reaction conditions :(i) dry acetone, 57°C, 4h, 32-97%.

Joachim Rudolph approach (2000)[18]

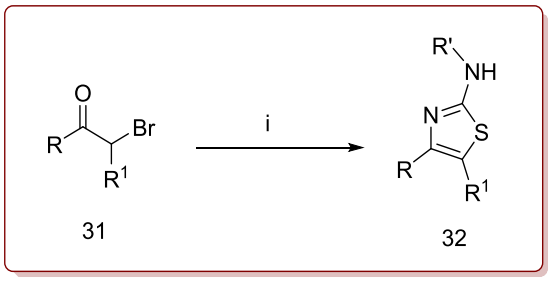
According to Joachim Rudolph, 2-aminothiazoles **30** were synthesised by reacting α-bromo the ketone group **27** using sodium thiocyanate **28** with amines **29** with ethanol in 50 °C for 7–15 hours.



Scheme 9. Reaction conditions: (i) NaSCN (28) with EtOH to50°C for 3h; (ii) R^1NH_2 (29), EtOH with a 50 °C,4-12 h;18-99%.

Mitsuo Kodomari et al. approach (2002)[19]

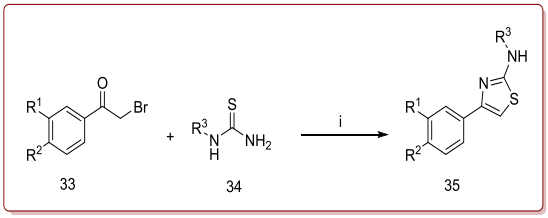
Mitsuo Kodomari and colleagues reportedon 2-aminothiazoles **32** were synthesied with alpha-bromo ketones **31** using the supported reagent system of $KSCN/SiO_2$-RNH_3OAc/Al_2O_3, wherein thealpha-bromo ketones **31** first responded in $KSCN/SiO_2$ to create an a α-thiocyano ketone, which was then treated with $R'NH_3OAc/Al_2O_3$ to afford 2-aminothiazole.



Scheme 10. Reaction conditions: (i) $KSCN/SiO_2$-$R'NH_3OAc/Al_2O_3$, benzene, 80°C, 6h, 46-96%.

Eduardo Garcia-Egido et al. approach (2002)[20]

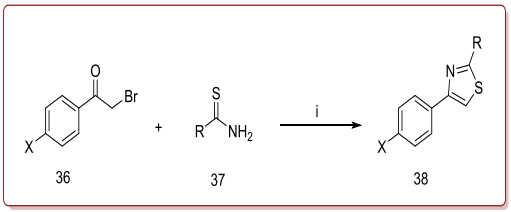
As reported by Eduardo Garcia-Egido et al., The chemical reactions of 1-methylpyrrolidin-2-one(NMP) the solution with 2-bromo-1-phenylethanone **33** the solution of NMP for 1-substitutingthiourea **34** a microreactor (500 V) with 70 °C in 30 minutes. 2-aminothiazoles **35** were synthesised.



Scheme 11. Reaction conditions: (i) NMP, 70°C, 30 min, 44-99%

K. Rama Rao et al. approach (2005)[21]

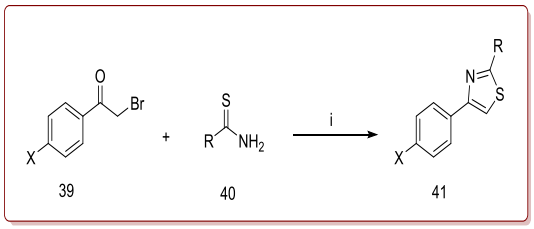
As reported by K. Rama Rao et al., 2-bromo-1-phenylethanone **36** and thioamide or thiourea **37** were combined with I-cyclodextrine by water in60°C for making thiazoles as well asaminothiazoles **38**.



Scheme 12. The reaction conditions: (i) *β*-cyclodextrin, H_2O, acetone, 50 °C,1 2.5 h, 80-92%.

Biswanath Das et al. method (2006)[22]

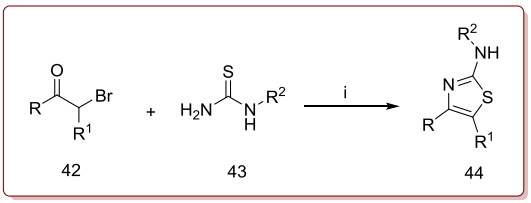
Ammonium 12-molybdophosphate was used as a catalyst in the author's report on the formation inthiazoles **41** by the condensed form of 2-bromo-1-phenylethanone **39** and thioamide **40** as methanol.



Scheme 13. Reaction conditions: (i) ammonium 12-molybdophosphate (AMP) with MeOH at rt 92-98%.

George W. Kabalka et al. approach (2006)[23]

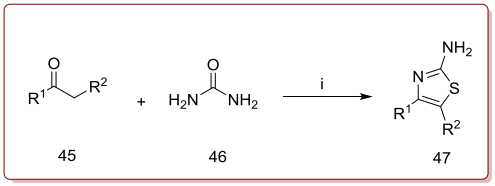
As reported by George W. Kabalka et al., 2-aminothiazoles **44** were synthesized using microwave-assisted condensation of thiourea **43** and alpha bromoketone **42.** The combination of bromo ketone and thiourea was microwaved for five minutes at 50 °C (100W).



Scheme 14. Reaction conditions :(i) MW(50°C, 100 W), EtOH, 5 min, 87-98%.

M. P. Kaushik et al. approach (2007)[24]

In a report by M. P. Kaushik et al., 2-aminothiazoles **47** were produced by mixing ketones **45** (1Eq) and thiourea **46** (2 Eq) with acetonitrile with silicate chloride catalyst (0.2 Eq) in 0 °C, the mixture was then refluxed for 1 hour.

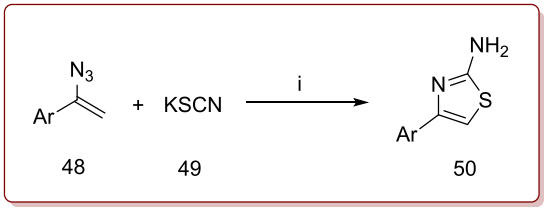


Scheme 15. Reaction conditions :(i) Silicate chloride, MeCN, 80 °C, 1h, 78-97%.

Y.Yu et al. approach (2015)[25]

In a report by Y. Yu. et al.,From vinylazides **48** and potassium thiocyanate **49**, palladium (II) acetate catalyses the

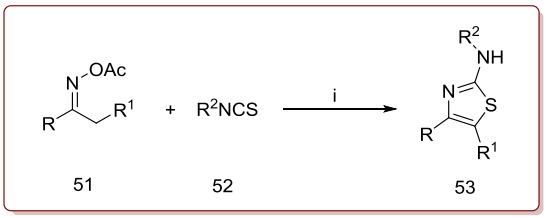
extremely selective synthesis of 4-substituted 2-aminothiazoles **50**.



Scheme 16. Reaction conditions: (i) 5 Mol % $Pd(OAc)_2$, PrOH, 80 °C, 12h, 42-94%.

H. Jiang et al. approach (2016)[26]

In a report by H. Jiang. et al.,Under moderate reaction conditions, copper-catalyzed N-O bond cleavage is used to couple oxime acetates **51** with isothiocyanates **52** to produce a variety of 4- and 4,5-substituted 2-aminothiazoles **53**.



Scheme 17. Reaction conditions: (i) CuI (20 mol%), Cs_2CO_3 (50 mol%) Toluene, Air 105 °C, 8h, 42-84%.

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