

Synthesis of 2-aminothiazole derivatives: A Short Review

Nitin L. Jadhao

Department of Chemistry, Late. N. P. W. College, Chopra (Mohadi), 441807, India.

Corresponding Author – Nitin L. Jadhao

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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 bacterial⁴ 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.

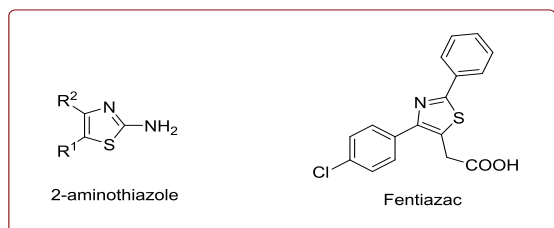


Figure 1. Structures of 2-aminothiazoles

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

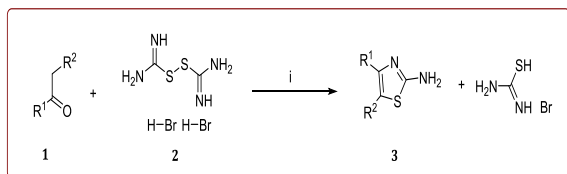
Previous Work:

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

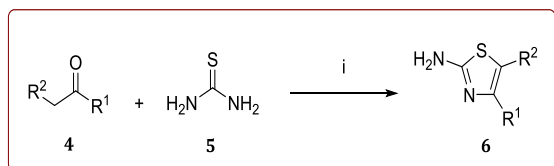
first used for producing formamidine disulfide dihydrobromide.



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

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

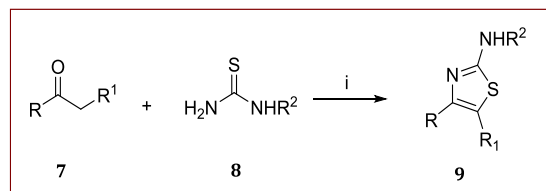
As reported by L. Carroll King et al., A combination with ketone **4** (1 eq.) and thiourea **5** (2 equiv), and iodine (1 equiv) produced 2-aminothiazoles **6**. In order to produce 2-aminothiazole derivatives, the reaction mixture contains the involved materials were heated overnight on a steam bath, 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 (I₂), 100°C (steambath), overnight, 18-97%.

H. K. Pujari et al. method (1986)¹²

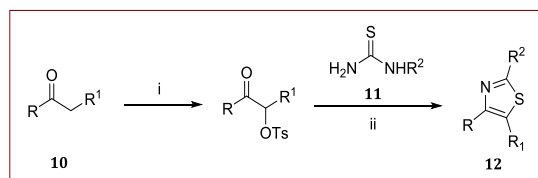
Applying N-bromosuccinimide (NBS), a catalytic quantity for benzoyl peroxide in the anhydrous form benzene at reflux conditions for a total of 6 hours on a steam bath, Pujari, H.K., and others described the synthesis is 2-aminothiazoles **9**. To get 2-aminothiazole, the hydrobromide salt that is produced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



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

Ram P. Kapoor et al. method (1993)¹³

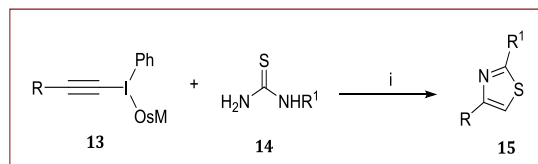
Ram P. Kapoor and colleagues described the formation for 2-substituted thiazoles **12** with reacting an enolisable ketone **10** using thallium (III) *p*-tolylsulfonate and a solvent in acetonitrile that is refluxing, following the use of thiourea or thioamide **11**. To get 2-substituted thiazoles,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



Scheme 4. Reaction conditions: (i) Thallium (III) *p*-tolylsulfonate (TTS), MeCN reflux 20-30min; (ii) MeCN, reflux, 1-2h, K₂CO₃, 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** and thioamide **14** in a solvent like Et₂O, EtOAc, or MeOH at 0°C for 3 hours.

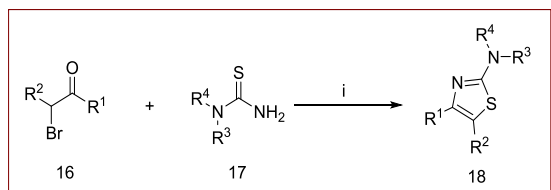


Scheme 5. Reaction conditions: (i) MeOH or Et₂O, carbonate or Et₃N, 3 h, 0°C, 32-64%.

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

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

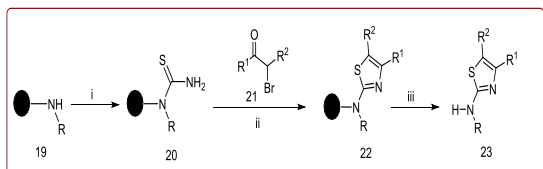
preparation process they used to synthesize 2-aminothiazoles **18** by reacting α -bromo ketones **16** and thiourea **17** were combined in DMF into 75 °C for 5 hours. A series of 2-aminothiazoles was produced in this manner.



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

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

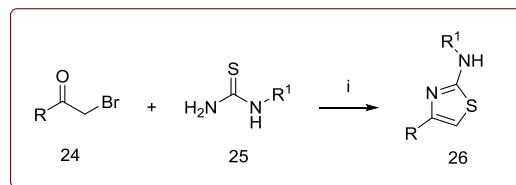
As reported by John A. Flygare and others synthesized 2-aminothiazole **23** began with resinbound amine, primary or secondary **19**. In the beginning, **19** interacted using 9-Fluorenylmethoxycarbonyl isothiocyanate (Fmoc-NCS) in produce thiourea that has been protected by Fmoc subsequent deprotection of Fmoc-group during simple circumstances produced pure thiourea **20**. Thiazoles **23** have been produced by reacting resin-attached thiourea **20** and a solution of dioxane containing α -bromo ketone group **21**.



Scheme 7. Reaction conditions: (i) fluorenylmethoxycarbonylisothiocyanate (Fmoc-NCS), DCM, rt, 30 minutes; 20% piperidine in methanol, overnight; (ii) dioxane, rt ; (iii) 95% TFA, 5% H₂O, 65-77%

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

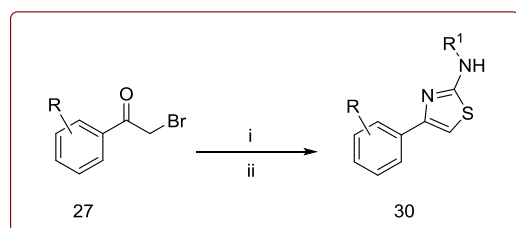
As reported by Simon S. W. Leung and coworkers, 2-aminothiazoles **26** were produced on heating a reaction mixture including in dry acetone at 57 °C, combine α -bromo ketone **24** with thiourea **25** for four hours.



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

Joachim Rudolph approach (2000)¹⁸

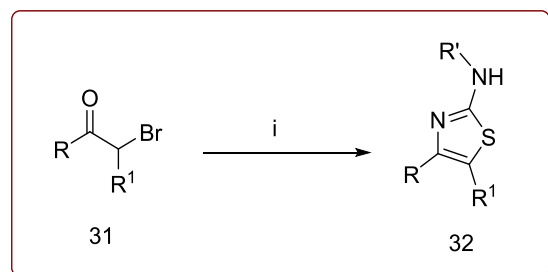
According to Joachim Rudolph, 2-aminothiazoles **30** were synthesised by reacting α -bromo ketone **27** using sodium thiocyanate **28** with amines **29** with ethanol in 50 °C for 7–15 hours.



Scheme 9. Reaction conditions: (i) NaSCN (28) with EtOH to 50°C for 3h; (ii) R¹NH₂ (29), EtOH with a 50 °C, 4-12 h; 18-99%.

Mitsuo Kodomari et al. approach (2002)¹⁹

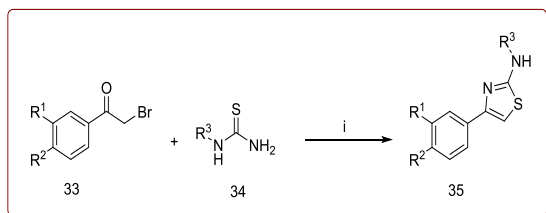
Mitsuo Kodomari and colleagues reported on 2-aminothiazoles **32** were synthesised with α -bromo ketones **31** using the supported reagent system of KSCN/SiO₂-RNH₃OAc/Al₂O₃, wherein the α -bromo ketones **31** first responded in KSCN/SiO₂ to create an α -thiocyanate ketone, which was then treated with R¹NH₃OAc/Al₂O₃ to afford 2-aminothiazole.



Scheme 10. Reaction conditions: (i) KSCN/SiO₂-R¹NH₃OAc/Al₂O₃, benzene, 80°C, 6h, 46-96%.

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

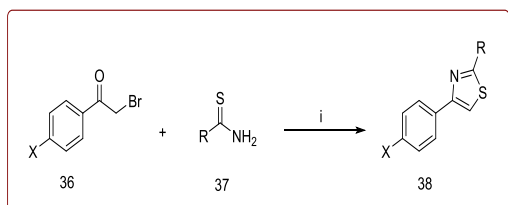
As reported by Eduardo Garcia-Egido et al., The chemical reactions of 1-methylpyrrolidin-2-one(NMP) the solution with 2-bromo-1-phenylethanone **33** the solution of NMP for 1-substitutingthiourea **34** a microreactor (500 V) with 70 °C in 30 minutes. 2-aminothiazoles **35** were synthesised.



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

K. Rama Rao et al. approach (2005)²¹

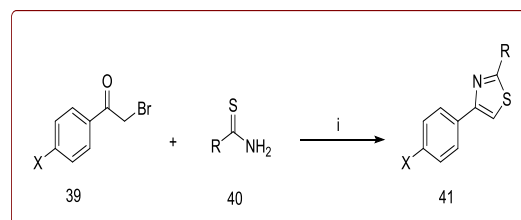
As reported by K. Rama Rao et al., 2-bromo-1-phenylethanone **36** and thioamide or thiourea **37** were combined with I-cyclodextrin by water in 60°C for making thiazoles as well as aminothiazoles **38**.



Scheme 12. The reaction conditions: (i) β -cyclodextrin, H₂O, acetone, 50 °C, 1.25 h, 80-92%.

Biswanath Das et al. method (2006)²²

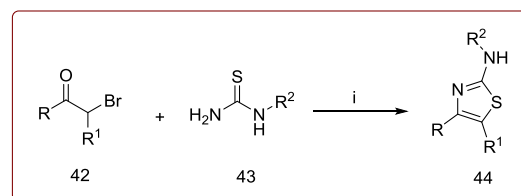
Ammonium 12-molybdophosphate was used as a catalyst in the author's report on the formation of thiazoles **41** by the condensed form of 2-bromo-1-phenylethanone **39** and thioamide **40** as methanol.



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

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

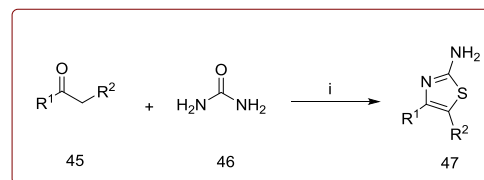
As reported by George W. Kabalka et al., 2-aminothiazoles **44** were synthesized using microwave-assisted condensation of thiourea **43** and alpha bromoketone **42**. The combination of bromo ketone and thiourea was microwaved for five minutes at 50 °C (100W).



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.

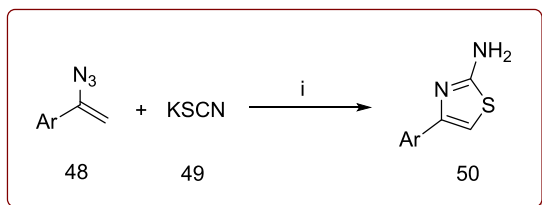


Scheme 15. Reaction conditions : (i) Silicate chloride, MeCN, 80 °C, 1h, 78-97%.

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

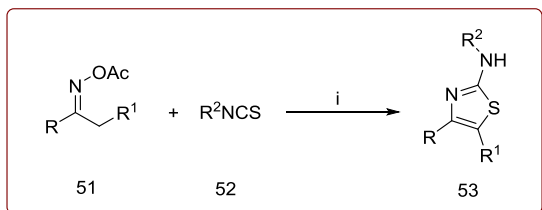
extremely selective synthesis of 4-substituted 2-aminothiazoles **50**.



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%), Cs₂CO₃ (50 mol%) Toluene, Air 105 °C, 8h, 42-84%.

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