International Journal of Engineering Research & Technology (IJERT)
ISSN: 2278-0181
Vol. 15 Issue 07 , July - 2026

Safety-Oriented Design of Tetrazole Synthesis in Pharmaceutical Manufacturing

Srikanth Reddy Jonnala
Department of Research and Development
Lee Pharma Limited
Visakhapatnam, Andhra Pradesh, India

Abstract - The Formation of Tetrazoles is from Nitriles and Sodium Azide. The reaction Mechanism, Can Proceed through Different Pathways depend on the Reaction Conditions. Generally, it Involves the Activation of nitriles Followed by a Nucleophilic Attack of the Azide ion (N_3^-) as R–C≡N + NaN_3 Here in Sodium Azide having N_3^- Electrons Having attack with Carbon then it is clearly azide attack on Nitrile Carbon to Formation of Tetrazole. This is Mostly Performed at Higher Temperatures and having a Significant in Pharmaceutical Drug Practices. This Reaction in Industrial scale having Explosion Hazard Chemicals like Sodium Azide as Thermally unstable with Regular Practice can leads a Explosive.so Better Practices makeup Development in Laboratory Scale through Optimum Temperatures ranges and Quenching Factors with Acids can Create a High Gas Liberation impact by Safe Approaching of this Preparation with Slow Addition Rate can Control the Reaction Rate in Large scale. These strategies enhance safety while maintaining efficiency, Venting Calculating approach, Proper Scrubbing media in Industrial Scale.

Keywords*: Tetrazole Synthesis, Sodium Azide, Hydrazoic Acid,*

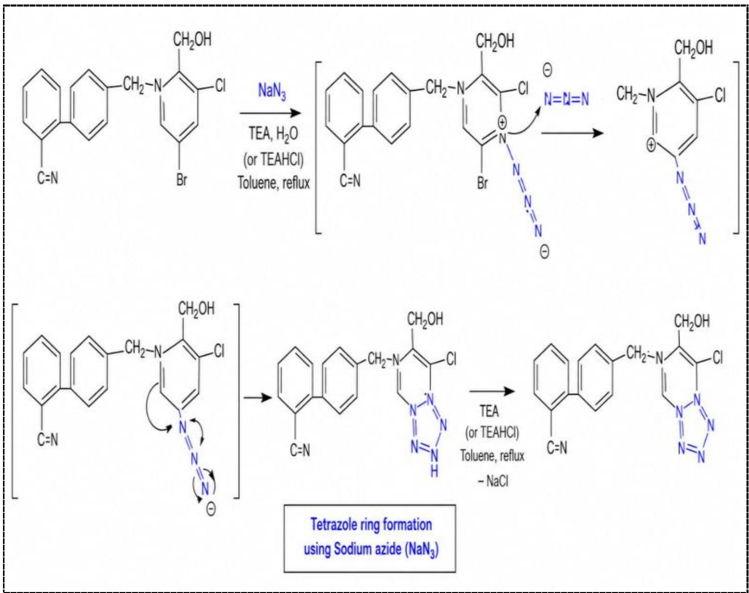
I. INTRODUCTION

Heterocyclic compounds form the backbone of modern drug discovery, with tetrazoles. A tetrazole ring consists of a five-membered heterocycle containing four nitrogen atoms and one carbon atom. Historically, strong mineral acids (such as sHCl or H_2SO_4) were employed for this protonation. This strategy introduces severe operational hazards [3], as strong acids violently displace the sodium cation to liberate hydrazoic acid (HN_3) gas [13]. Hydrazoic acid is notoriously toxic upon inhalation and highly unstable, carrying a severe risk of spontaneous vapor-phase detonation when heated or concentrated in reaction [11]. To resolve these pressing safety concerns without compromising chemical yield, specifically triethylamine hydrochloride (TEA·HCl). The triethylammonium cation acts as a mild, buffered proton donor that establishes a steady, controlled equilibrium in solution that Refers the Chemical Equation:

$$(C2H5)_3NH^+Cl^-_{(aq)} + NaN3^-_{(aq)} \longrightarrow HN3_{(g)} + (C2H5)3N^+$$

When hydrochloric acid is mixed with sodium azide it undergoes an acid-base displacement reaction that generates hydrazoic acid Hydrazoic acid is a highly volatile liquid that readily vaporizes, liberating a highly toxic, colorless, and explosive gas [13]. Here the Thermodynamic properties are Considered as a Safety Module. Before an explosion we Must Take a Safety precautionary Action. The Major Issue in This Tetrazole Formation is Liberat ion of Hydrazoic Acid (HN_3) Gas with highly Volatile and ready to Vaporizes into Colorless Gases [6].

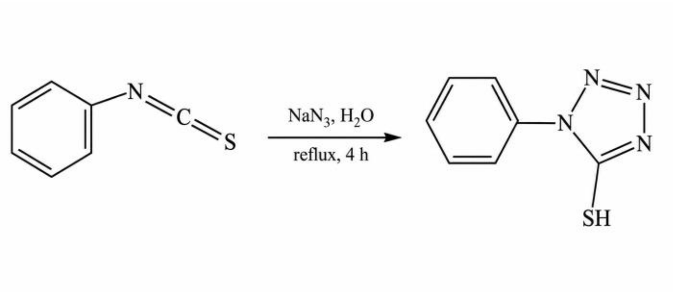
Molecular weight=43.03g/mol
Boiling Point: 37°C
Melting point: -80°C
Density: 1.09 g/cm3 at 25°C
Standard Enthalpy of Formation (Δ $_f$ H): +294 kj/mol
This highly positive heat of formation indicates that the molecule is thermodynamically unstable [5].



II. LITERATURE REVIEW:

2.1 Historical Context:

In their seminal 1958 work, Finnegan, Henry, and Lieber (J. Am. Chem. Soc.) established the baseline method for this condensation using sodium azide (NaN_3) paired with ammonium chloride (NH_4Cl) as an acidic promoter in N,N-dimethylformamide (DMF) as Solvent [14].



2.2 Comparison Of Alternative Methods:

Method	Reagents	Advantages	Disadvantages
Finnegan Method	NaN_3+NH_4Cl	Cheap, Fast Reaction Rates	High Explosion Risk
Amine Salt	NaN3 +TEA. HCL	Safe to Scaleup	Generate Small Amount of Volatile NH3
Lewis Acid	NaN_3+$ZnCl_2$ +$AlCl_3$	Neutralize the NH3 Gas	Requires Heavy Metals
Silicon Azides	TMS-N3/ Fluoride Catalyst	No Metal Salts Required	Extremely Expensive Reagents, Water Sensitive

2.3 Conclusion:

This literature review contextualizes the TEA· HCl protocol as the direct solution to the historical safety hazards. The combination of TEA·HCl and NaN_3 remains a good Methods in modern Industrial chemical process [4]. It cleanly Gives a balance between operational Easier, high conversion yields, and enhanced thermal process safety, making it a staple strategy for Large Scale Synthesis.

III. METHODOLOGY

3.1 Estimation of HN_3 Generation:

Before Getting into Technical Calculation initially we Start with Mole For Our Basical Reaction for that we have Limiting reagent is Sodium Azide that I Takes as a Reference to Calculate this generation of Byproduct Quantities.

$(C2H5)_3NH^+Cl^-$ + $NaN3^-$ ⟶ HN3 + $(C2H5)3N^+$

	$(C2H5)_3NH^+Cl^-$	$NaN3^-$	HN3	$(C2H5)3N^+$
Weight	168 Kg	72 Kg	47.63 Kg	112.017 kg
Mol.wt	137.65 g/Mol	65.009 g/mole	43.029 g/mole	101.19 g/mole
No, of Moles	1.2204 k. mole	1.107 k.mole	0.263 k.mole	0.263 k.mole

Here one More Important thing is after Completion of reaction we must surely check Measuring Residual Sodium Azide (NaN_3) in Reaction Mass. That we want to check in "Ion Chromatography" because it directly measures the azide ion with good accuracy.

3.2 Gas Release Rate Determination:

Here that I Estimated HN3 Gas 47 Kg's is Release Rate is 5 Minutes. So, Flowrate is 47 Kg's/ 5 Min = 9.4 Kg/Min then Convert into Kg/Sec = 9.4 Kg/60 = 0.1566 Kg/sec

- **Pressure (P)=** (101,325 Pa) (Atmospheric pressure)
- **Gas Constant (R)**= 8314 J/(kmol.K)
- Molecular Weight(M) = 43.03 g/mol

3.3 Gas density Estimation:

Here we Have to Estimate in the Gas Density By using IDEAL GAS EQUATION:

$\rho = P \times M / R \times T$

ρ =(101,325 pa×43.03 g/mol) /(8314 j/(kmol.K) × 368 K

$\boldsymbol{\rho = 1.42\ kg/m^3}$

3.4 Minimum Vent Area Calculation:

Volumetric Flowrate (Q):

Q = W/ ρ

= (0.1566 Kg/sec) / (1.42 kg/m^3)

Q = 0.11032 m^3/Sec

Calculate Minimum Vent Cross Sectional Area:

Area (A) = Q / V

Area (A) = (0.11032 m^3/Sec) / (15 m/s)

Area (A) = 0.007354 m2

Calculate Inner Diameter:

Area(A) = $\pi \times D^2 / 4$

$D^2 = \sqrt{4 \times \text{Area}} / \pi$

D = 0.0967 m

D = 96.74 mm

Convert into Inch 96.74 mm × 0.03937 = 3.80"

Then Prefer 4" Vent Line Is Required fir this Reaction.

3.5 Neutralization of HN3 Content with safety Precautionary Action:

After Completion of Reaction conversion and form tetrazole Ring. Then there a Chance For HN3 Traces in Reaction Mass Because This reaction converts volatile, acidic HN_3 into its ionic form (azide ion, N_3^-) in alkaline solution. In industrial settings, maintaining an alkaline environment helps reduce the amount of HN_3 present in solution [2]. The Practical Solution Behind for this Problem is Improving the NaoH Workup Here Tetrazoles are acidic compounds [1]. When NaOH is added,

International Journal of Engineering Research & Technology (IJERT)
ISSN: 2278-0181
Vol. 15 Issue 07 , July - 2026

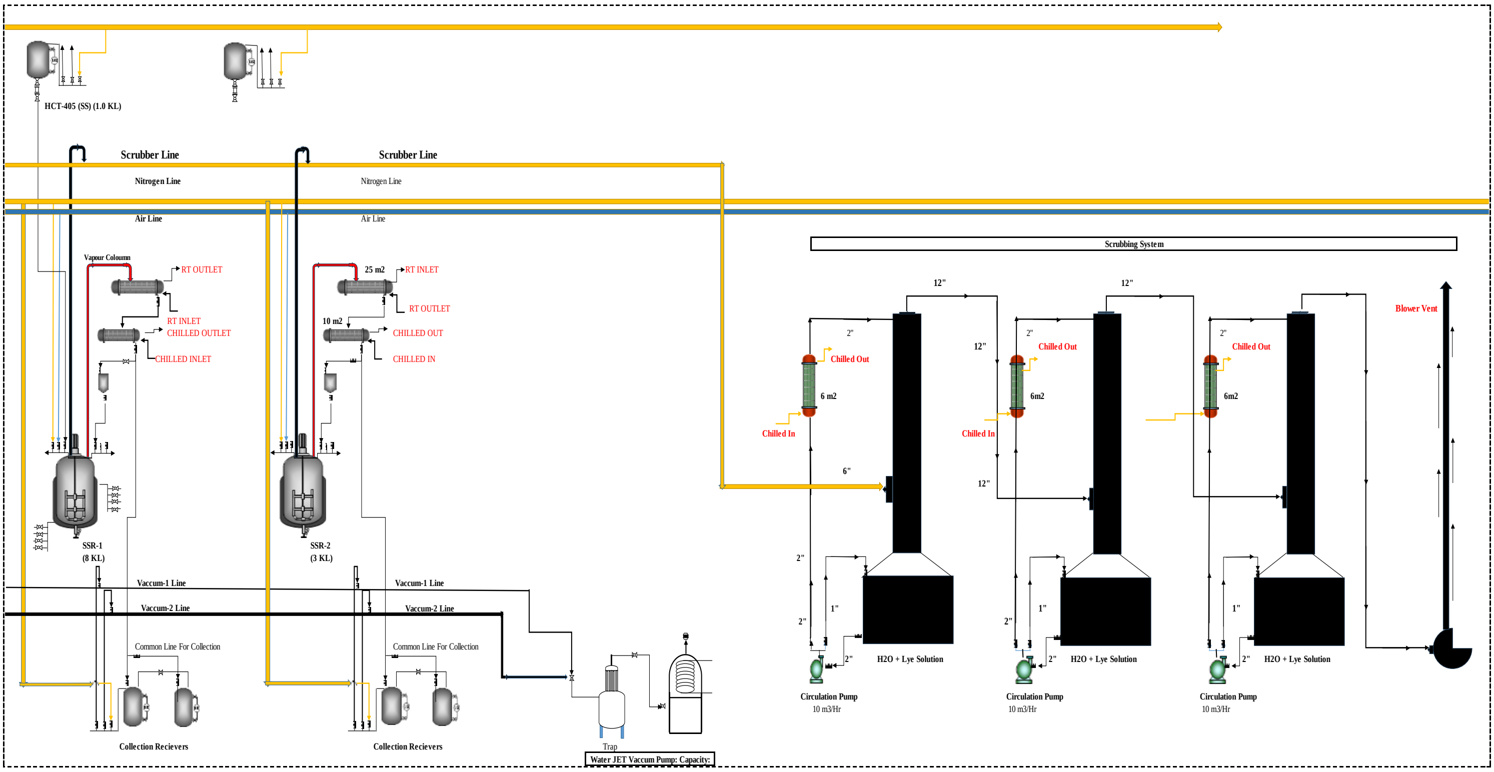


Fig.1 Industrial Scale Piping & Instrumentation Diagram

the tetrazole is converted to its tetrazole sodium salt, which is generally much more soluble in the aqueous phase than in toluene. This allows it to be separated from neutral organic impurities. In a later step, the product may be acidified again to regenerate the free tetrazole, if required. Any remaining HN_3 is converted by NaOH into sodium azide [8].

HN3 + NaOH ⟶ NaN3 + H2O

Sodium azide is highly water-soluble, so it partitions into the aqueous phase. his step reduces the amount of volatile HN_3 in the reaction mixture.

Here there having a Chance by Forming of Nacl Salts that mostly dissolves in Aqueous Layer. Finally Process Safety Concerns are Performed for Maintaining alkaline conditions minimizes the presence of volatile HN_3[10] , reducing the risk of hazardous vapor formation during work-up.

3.6 Requirement of Scrubber:

Before Getting into the calculation I Previously Mentioned That Flowrate Estimation is **m=0.1566 Kg/sec** and gas Density is Calculated by using Ideal Gas equation is ρ=**1.42 Kg/m3**

Calculation: $Q = \dot{m} / \rho$

$Q = 0.1566$ Kg/sec / 1.42 Kg/m^3

$Q = 0.1103$ m^3/sec

Then Convert into Kg/sec:

$Q = 0.1103$ Kg/Sec × 3600

$Q = 397$ m^3/Hour

Then Convert into CFM:

CFM= 397 m^3/Hour × 0.588

CFM = 233.43

Then finally we Have requirement of 233 CFM of Scrubber

3.7 NaOH Requirement:

HN3 + NaOH ⟶ NaN3 + H2O

Moles of HN_3:

n = 47000 g/43.03 g/mol

n = 1092.26 mol

NaOH Required= 1092.26 mol × 40 g/mol

=43680 g.

Convert in Kg's is 43.68 Kg's

Here I Take 25% if Excess Quantity

Required Quantity= 43.68 kg × 1.25

Required Quantity NaOH= 54.6 Kg's

3.8 Estimation of Lye Solution Volume in Scrubber:

Generally, in Industrial Cases we prepare 10% of NaOH Solution.

Required Quantity of NaOH= 54.6 Kg's

Solution Required = 54.6 /0.10

Solution Required = 546 kg's

Since the Density = 1.11 kg/L

Solution Volume (V) = 546 kg/1.11 kg/L

Solution Volume (V) = 491.85 L

Here Recommendation is

500 L of 10 wt.% NaOH solution

IV. RESULTS & GRAPHS:

4.1 Vent Sizing Results:

Parameter	Value
HN_3 Generated	47 Kg
Gas Release Time	50 min
Mass Flowrate	9.4 Kg/min
Gas Density	1.42 Kg/m^3
Volumetric Flowrate	0.1103 m^3/sec
Required Vent Area	0.00735 m^2
Calculated Diameter	96.77 mm

International Journal of Engineering Research & Technology (IJERT)
ISSN: 2278-0181
Vol. 15 Issue 07 , July - 2026

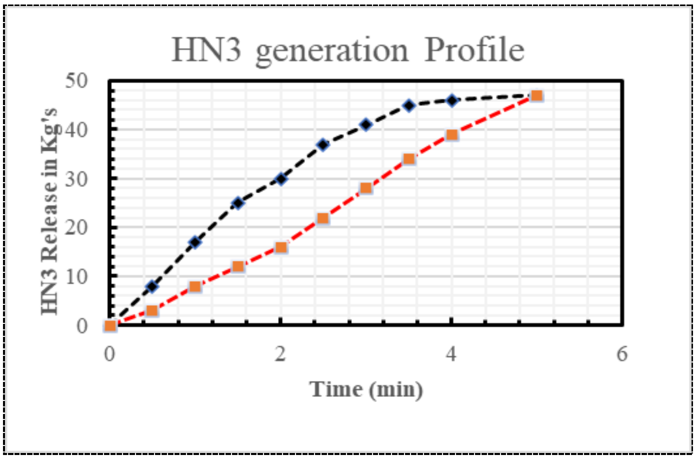
Recommended Vent Size	4 Inch

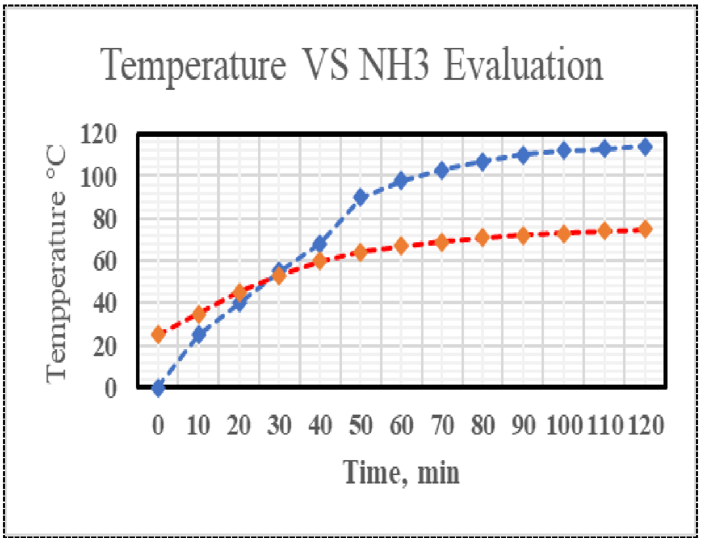
4.2 Scrubber Design Result's:

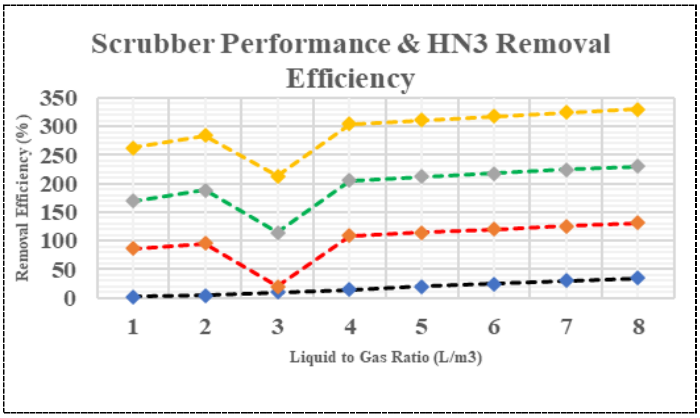
Parameter	Value
Gas	Hydrazoic Acid
Total HN_3 Released	47 Kg's
Release Time (Estimation)	5 Min
Gas Release Rate	9.4 Kg/min
Operating Pressure	1 atm
Operating Temperature	95°C
Molecular Weight	43.03 /mol

4.3 Overall Process Comparison:

Parameter	Convectional (HCL/NH_4Cl)	Proposed (TEA.HCL)	Improvement
HN_3 Released	High	Controlled	High
Max Temperature	110°C	70°C	Excellent
Vent Size	6''	4"	Good
NaoH Required	High	54.6 Kg	Good
Scrubber Effiency	90-95%	99%	Excellent
Overall Safety	Low	High	Excellent







V. REFERENCES

[1] Finnegan, W. G., Henry, R. A., and Lieber, E., "A New Synthesis of Tetrazoles," *Journal of the American Chemical Society*, vol. 80, no. 15, pp. 3908–3911, 1958.

[2] March's Advanced Organic Chemistry, 7th ed., Wiley, 2013.

[3] Comprehensive Heterocyclic Chemistry III, Vol. 5, Elsevier, 2008.

[4] National Institute for Occupational Safety and Health, *Hydrazoic Acid (HN_3): Pocket Guide to Chemical Hazards*.

[5] Occupational Safety and Health Administration, *Hydrazoic Acid Safety Data and Occupational Exposure Information.*

[6] National Fire Protection Association, *NFPA 68: Standard on Explosion Protection by Deflagration Venting*, Latest Edition.

[7] National Fire Protection Association, *NFPA 69: Standard on Explosion Prevention Systems*, Latest Edition.

[8] American Society of Mechanical Engineers, *ASME Boiler and Pressure Vessel Code, Section VIII – Pressure Relief Devices.*

[9] American Institute of Chemical Engineers, *Guidelines for Pressure Relief and Effluent Handling Systems*, Center for Chemical Process Safety (CCPS).

[10] American Institute of Chemical Engineers, *Guidelines for Hazard Evaluation Procedures*, 3rd ed.

[11] Perry's Chemical Engineers' Handbook, 9th Edition, McGraw-Hill Education.

[12] National Institute of Standards and Technology, *NIST Chemistry Webbook: Hydrazoic Acid Physical and Thermodynamic Properties.*

[13] PubChem, "Hydrazoic Acid (HN_3)," National Library of Medicine.

[14] Bretherick's Handbook of Reactive Chemical Hazards, 8th Edition, Elsevier.

15] Center for Chemical Process Safety, *Layer of Protection Analysis: Simplified Process Risk Assessment.*