Research Journal of Recent Sciences _____ ISSN 2277 - 2502
Vol. **1(ISC-2011),** 79-84 **(2012)** *Res.J.Recent.Sci.*

Synthesis, characterization and de-tert-butylation of 4-N-t-butyl-5-aryl imino-1,2,4 triazolidine-3-thiones into 5-arylimino-1,2,4 triazolidine-3-thiones

Rashidi N.A and Berad B.N
Department of Chemistry, Shri Shivaji Science College, Amravati, MS, INDIA
Department of Chemistry, RTM Nagpur University, Nagpur, MS, INDIA

Available online at: www.isca.in
(Received 10th October 2011, revised 10th January 2012, accepted 24thJanuary 2012)

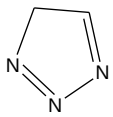
Abstract

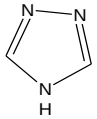
Triazole is a five membered heterocyclic ring which is a versatile lead compound for designing potent bioactive agents. The derivatives of triazole nuclei showed diverse biological activities. In the present study, we have synthesised some new 4-N-t-butyl-5-arylimino-1,2,4-triazole-3-thiones (Va-f) from 2-arylimino-5-t-butylimino-1,3,4-thiadiazoles (IVa-f).The later compound were prepared by the condensation of N-aryl thiosemicarbazide (IIa-f) and tert-butyl imino isocyanodichloride in chloroform medium. The synthesized compounds (Va-f) were successfully de-tert butylated into 5-arylimino-1,2,4-triazolidine-3-thione (VIa-f). All the newly synthesized compounds were subjected to physical characterization and spectral analysis by IR and NMR and Mass for structure elucidation.

Keywords: 1,2,4-triazole 1,3,4-thiadiazole, Aryl isothiocyanate, N-t-butyl isocyanodichlorides.

Introduction

The chemistry of heterocyclic compounds continues to be an active field in the organic chemistry. Triazole derivatives have occupied an unique position in heterocyclic chemistry due to their biological activities[1-3]. Triazole is any five-membered heterocycle having two carbon, three nitrogen atoms and two double bonds having general formula $C_2H_3N_3$.The two isomers are 1,2,3-triazole and 1,2,4-triazole.


1,2,3-triazole


1,2,4-triazole

Out of the two triazoles 1, 2, 4- triazole has wide variety of activity[4-5] .1,2,4-Triazoles as antibacterial agents can be grouped according to the mode of action, i.e. the ability to inhibit the synthesis of the cell wall, cell membrane, proteins and nucleic acids of bacteria. The synthesis of 1, 2, 4-triazoles has also attracted wide spread attention due to the diverse agricultural (such as fungicidal, insecticidal, bactericidal, herbicidal) and industrial activities (dyes, lubricants and analytical reagents, antiviral agents), including anti-inflammatory, analgesic, antitumoral, anticonvulsant and tranquilizing activities shown by these compounds[6-8]. Examples of such compounds bearing the 1,2,4-triazole moieties are fluconazole, a powerful azole antifungal agent. In view of these observations, in the present study we have synthesized some new derivatives of 1,2,4-triazoles. The synthesized compounds were subjected to physical characterization and spectral analysis by IR, NMR and Mass for structure elucidation.

Material and Methods

All the chemicals were purchased from local market and purified according to established method. Melting points were recorded using VEEGO digital melting point apparatus. The homogeneity and purity of synthesized compounds was established by thin layer chromatography (TLC). Precoated silica gel aluminium plate (20 cm x 20 cm with 250 µm thickness were used for TLC (E. Merck). Iodine was used to develop the TLC plates. Infrared (IR) spectra were recorded on Perkin Elmer FT-IR spectrophotometer model using nujol and potassium bromide pellets (õmax in cm^{-1}). ^{1}HNMR spectra were recorded on Brucker Advance II 400 NMR spectrometer using deuterated dimethyl sulfoxide-containing tetramethyl silane (Me_4Si) as internal standard (chemical shifts in ó, ppm). The Mass spectrum was recorded on TOF MS ES+ Mass spectrometer.

Six substituted aryl isothiocyanate (Ia-f) were synthesized by the reaction of corresponding amines with carbon disulfide and ammonium hydroxide by following the reported method [9].Tert-butyl isothiocyanate was prepared by known procedure[10].

Preparation of t-butyl imino isocyanodichloride[11]: Through a chloroform solution of t-butyl isothiocyanate (6ml in 15ml) chlorine (generated from 10gm $KMNO_4$ and 70 ml conc. HCl) was passed maintaining the temperature at 15^0. After addition of chlorine had been completed, the yellow

reaction mixture was diluted with 40 ml dry petroleum ether (60^0-80^0) and filtered to remove suspended impurities. The solvent was then removed by distillation under vaccum. The whole operation is repeated with 40 ml petroleum ether and finally petroleum ether solvent was distilled off, t-butyl iso cyanodichloride (10 ml) in the form of yellow oil was collected.

Synthesis of N-p-tolyl thiosemicarbazide[12,13] (IIa): Dissolved p-tolyl iso thiocyanate (Ia) as (0.01 mol) in 20 ml chloroform and hydrazine hydrate (99%) (0.01 mol) was added drop wise to the reaction mixture with stirring. The reaction was found to be exothermic. The resulting mixture was allowed to cool. The white solid separated within 10 minutes, was filtered, washed with water and dried. Recrystallised the product (IIa) with ethanol. The above reaction was extended to synthesize compounds (IIb-f)

Synthesis of 2-p-tolylimino- 5-N-t-butylimino-1, 3,4-thiadiazoles (IVa): The N-p-tolyl thiosemicarbazide (IIa) and t-butyl imino isocyanodichloride in equimolar proportion were refluxed in chloroform medium for 3 hr. The evolution of hydrogen chloride gas was observed. After completion of reaction, distilled off solvent, afforded a sticky mass which on washing with petroleum ether (60^0- 80^0) followed by addition of little amount of ethanol gave a pale yellow solid. It was crystallized from ethanol. The resultant solid was found to be mono hydrochloride (IIIa). Basification of it with aqueous ammonia afforded a free base (IVa), crystallized from aqueous ethanol (70%), m.p 102^0C. The product was soluble in organic solvent but insoluble in water and gave positive test for N and S elements.

On extending the above reaction to other N-aryl thiosemicarbazide, the related 1,3,4-thiadiazoles were isolated in good yield.

(**IVa**) : **IR spectra**[14]: (KBr) cm-1: 3392 (NH), 3228(NH), 3180-3112(Ar-H), 3026-2980 (C-H, t-Bu), 2918,2856(C-H),1487 (C=N), 1313 (C-N), 810 (C-S); **1H-NMR** (DMSOd6) ppm: 1.2-1.6 (9H, m, t-Bu), 2.1(3H, s, CH_3) 6.92-7.2 (4H, m, Ar-H), 7.3 (1H, d, NH), 7.4(1H, d, NH) (**IVc**) IR: (KBr) cm-1 3391(N-H) 3195-3138(Ar-H), 2969-2795 C-H),1613 (C=N), 1167 (C-N), 774(C-S); **1H-NMR** (DMSOd6) ppm: 1.2-1.6 (9H, m, t-Bu), 2.1(3H, s, CH_3) 6.92-7.2 (4H, m, Ar-H), 7.4 (1H, d, NH), 8.4(1H, d, NH)

Synthesis of 4-N-t-butyl-5-p-tolyl imino-1,2,4-triazolidine-3-thiones (Va) : The 2-p-tolylimino- 5-N-t-butylimino-1,3,4-thiadiazoles (IVa) were refluxed with 5% ethanolic NaOH for 1.5 hr, where the compound (IVa) underwent isomerisation. After completion of reaction, the reaction mixture was cooled and poured in ice crushed water. The solid that separated was collected, dried and crystallized from ethanol, m.p122^0C. The product (Va) was soluble in organic solvent but insoluble in water. Sulphur and nitrogen element test gave the positive result for the product.

The above reaction was extended to synthesize compounds (Vb-f) **(Va) : IR spectra** :(KBr) cm-1 : 3392 (N-H), 3238(N-H), 3183-3111(Ar-H),3031-2959 (C-H,t-Bu), 2917,2849(C-H,CH_3),1514(C=N), 1316 (C-N), 1218(C=S) **(Va) : Mass (m/z)** : 264 [M+], 207, 192, 163,133

(Vc) IR spectra: (KBr) cm-1 : 3198 (N-H), 3139 (Ar-H), 2955-2849 C-H),1485 (C=N), 1295(C-N), 1262(C=S) **1H-NMR** (DMSOd6) ppm: 1.2-1.6 (9H, m, t-Bu), 2.1(3H,s,CH_3) 6.92-7.2 (4H, m, Ar-H), 7.4 (1H, d, NH), 8.4(1H, d, NH)

Synthesis of 5-p-tolyl imino-1,2,4-triazolidine-3-thiones (VIa): The product 4-N-t-butyl-5-p-tolyl imino-1,2,4-triazolidine-3-thiones (Va) when subjected to hydrolysis with boiling 30% sulphuric acid under reflux for 3 hr, the solid gradually went into solution and a clear solution was obtained. After completion of reaction, the reaction mixture was cooled and poured in ice crushed water. The product that separated was collected, dried and crystallized. The product obtained was found to be de-tert-butylated[15] (IVa), m.p 142^0C and gave positive test for N and S elements.The above reaction was extended to synthesize compounds (VIb-f)

(VIa) ^{1}H-NMR: (DMSOd6) ppm : δ 2.2 (3H, s, CH_3), 7.00 (2H, d, Ar-H) 7.3(2H, d, Ar-H), 4.9(2H, N-H) and 10.2 ppm (1H, s, N-H);

Results and Discussion

Six substituted aryl isothiocyanate (Ia-f) were synthesized by the reaction of corresponding amines with carbon disulfide and ammonium hydroxide. The N-aryl thiosemicarbazides (IIa-f) were prepared by the treatment of isothiocyanate with hydrazine hydrate in chloroform medium[11]. The condensation of N-p-tolyl thiosemicarbazide (IIa) with t-butyl imino isocyanodichloride in chloroform was carried out for 3 hr. The evolution of hydrogen chloride gas was observed and tested with moist blue litmus paper. Cooling the reaction mixture and distilling off the solvent afforded a sticky mass, which on washing with petroleum ether followed by addition of a little ethanol gave a light yellow solid. It was crystallized from aqueous ethanol (70%), m.p $72\text{-}74^0$C. It was acidic to litmus. On determination of equivalent weight it was found to be mono hydrochloride (IIIa). On basification with ammonium hydroxide, afforded a free base (IVa) crystallized from aqueous ethanol, m.p102^0C. On the basis of spectral data IR and 1H NMR and above facts the compound (IVa) has been assigned the structure as 2-p-tolyl imino-5-t-butylimino-1,3,4-thiadiazole.

The other compounds (IVb-f) were prepared by extending the above reaction to other N-aryl thiosemicarbazides (IIb-f) and the related 1,3,4-thiadiazole (IVb-f) were isolated in good

yield (table1). The product (IVa) was allowed to react with 5% ethanolic NaOH at reflux for 1.5 hr where it underwent isomerization. On the basis of elemental data and spectral analysis of isomerised product (Va), it was found to be 4-N-t-butyl-5-arylimino-1,2,4-triazolidine-3-thione. The Mass spectra of compound (Va) showed [M+] peak at m/z 264 and a base peak at m/z 207(100%).The other compounds (Vb-f) were prepared by following the similar method (Table 2).

The resultant product (Va) was further converted into 5-p-tolyl imino-1,2,4-triazolidine-3-thione (VIa) by refluxing with 30% sulphuric acid underwent de-t-butylation. The structure of 5-p-tolyl imino-1,2,4-triazolidine-3-thione (VIa) was confirmed by $_1$H NMR spectral data. The $_1$H NMR spectra of 4-N-t-butyl-5-p-tolyl imino-1,2,4-triazolidine-3-thione (Va) showed a multiplet in the range 1.2-1.6 attributed to the C-H of t-butyl group. The absence of signals due to C-H of t-butyl group in $_1$H NMR spectra of product (VIa) confirmed that compound (Va) was successfully de-tertbutylated into 5-arylimino-1,2,4-triazolidine-3-thione (VIa). The above reaction was extended to synthesize compounds (VIb-f) (table 3). The elemental analysis and spectral data IR, ^{1}H-NMR and Mass of all the synthesized compounds was in full agreement with the proposed structures. The synthetic route is outlined in *Scheme*. (fig 1)

PHYSICAL CHARACTERISATION

Table-1
Formation of 2-Arylimino- 5-N-t-butylimino-1,3,4-thiadiazoles (IV)
Reagent : Aryl thiosemicarbazide(II) and t-butyl imino isocyanodichloride

Aryl thiosemicarbazide(II)	2-Aryl imino- 5-N-t-butylimino-1,3,4-thiadiazoles hydrochlorides(III).	Yield %	M.P ^{0}C	Eq. wt. Found (calcd)	2-Aryl imino- 5-N-t-butylimino-1,3,4-thiadiazoles (IV) (Free base).	M.P ^{0}C	N % Found (Calcd)
p-Tolyl thiosemicarbazid(IIa)	2-p-Tolyl imino- 5-N-t-butylimino-1,3,4-thiadiazoles hydrochlorides(IIIa).	78	72-74	296.3 (298.8)	2-p-Tolyl imino-5-N-t-butylimino-1,3,4-thiadiazoles (IVa).	102	21.30 (21.35)
Phenyl thiosemicarbazide(IIb)	2-Phenyl…..1,3,4-thiadiazole hydrochloride(IIIb)	80	96-98	282.8 (284.8)	2-Phenyl imino-5-N-t-butylimino-1,3,4-thiadiazole (IVb)	144	22.50 (22.56)
o-Tolyl thiosemicarbazide(IIc)	2-o-Tolyl…..1,3,4-thiadiazole hydrochloride(IIIc)	75	88-90	297.3 (298.8)	2-o-Tolyl imino-5-N-t-butylimino-1,3,4-thiadiazole (IVc)	115	21.33 (21.35)
m-Tolyl thiosemicarbazide(IId)	2-m-Tolyl…..1,3,4-thiadiazole hydrochloride(IIId)	67	80-82	295.4 (298.8)	2-m-Tolyl imino-5-N-t-butylimino-1,3,4-thiadiazole(IVd)	164	20.60 (21.35)
o-Chloro thiosemicarbazide(IIe)	2-o-Chloro phenyl….1,3,4-thiadiazole hydrochloride(IIIe)	65	93-95	317.4 (319.2)	2-o-Chloro phenyl imino-5-N-t-butylimino-1,3,4-thiadiazole(IVe)	110	19.05 (19.81)
p-Chloro thiosemicarbazide(IIf)	2-p-Chloro phenyl….1,3,4-thiadiazole hydrochloride(IIIf)	81	60-62	316.1 (319.2)	2-p-Chloro phenyl imino-5-N-t-butylimino-1,3,4-thiadiazole (IVf)	156	19.77 (19.81)

Note: All the compounds gave satisfactory C, H, Cl, and S analysis

Table-2
Formation of 4-N-t-butyl-5-aryl imino-1,2,4-triazolidine-3-thiones(V)
Reagent : 2-Aryl imino- 5-N-t-butylimino-1,3,4-thiadiazoles (IV) and NaOH in ethanol (5%).

2-Aryl imino- 5-N-t-butylimino-1,3,4-thiadiazoles (IV).	**4-N-t-butyl-5-aryl imino-1,2,4-triazolidine-3-thiones(V)**	**Yield %**	**M.P ^{0}C**	**Mol Formula**	**N % found (Calcd)**
2-p-Tolyl imino- 5-N-t-butylimino-1,3,4-thiadiazoles (IVa).	4-N-t-butyl-5-p-tolyl imino-1,2,4-triazolidine-3-thiones(Va)	73	122	$C_{13}H_{18}N_4S$	21.50 (21.35)
2-Phenyl imino-5-N-t-butylimino-1,3,4-tiadiazole (IVb)	4-N-t-butyl-5-phenyl imino-1,2,4-triazolidine-3-thiones(Vb)	80	141	$C_{12}H_{16}N_4S$	22.10 (22.56)
2-o-Tolyl imino-5-N-t-butylimino-1,3,4-tiadiazole (IVc)	4-N-t-butyl-5-o-tolyl imino-1,2,4-triazolidine-3-thiones(Vc)	70	168	$C_{13}H_{18}N_4S$	20.60 (21.35)
2-m-Tolyl imino-5-N-t-butylimino-1,3,4-tiadiazole (IVd)	4-N-t-butyl-5-m-tolyl imino-1,2,4-triazolidine-3-thiones(Vd)	71	185	$C_{13}H_{18}N_4S$	21.32 (21.35)
2-o-Chloro phenyl imino-5-N-t-butylimino-1,3,4-tiadiazole (IVe)	4-N-t-butyl-5-o-chloro phenyl imino-1,2,4-triazolidine-3-thiones(Ve)	67	136	$C_{12}H_{15}ClN_4S$	19.16 (19.81)
2-p-Chloro phenyl imino-5-N-t-butylimino-1,3,4-tiadiazole (IVf)	4-N-t-butyl-5-p-chloro phenyl imino-1,2,4-triazolidine-3-thiones(Vf)	78	166	$C_{12}H_{15}ClN_4S$	19.77 (19.81)

Note: All the compounds gave satisfactory C, H, Cl, and S analysis

Table 3
Formation of 5-Aryl imino-1,2,4-triazolidine-3-thiones(VI).
Reagent : 4-N-t-butyl-5-aryl imino-1,2,4-triazolidine-3-thiones(V) and 30% H_2SO_4.

4-N-t-butyl-5-aryl imino-1,2,4-triazolidine-3-thiones(V)	**5-Aryl imino-1,2,4-triazolidine-3-thiones (VI)**	**M.P ^{0}C**
4-N-t-butyl-5-p-tolyl imino-1,2,4-triazolidine-3-thiones(Va)	5-p-Tolyl imino-1,2,4-triazolidine-3-thiones (VIa)	142
4-N-t-butyl-5-phenyl imino-1,2,4-triazolidine-3-thiones(Vb)	5-Phenyl imino-1,2,4-triazolidine-3-thiones (VIb)	134
4-N-t-butyl-5-o-tolyl imino-1,2,4-triazolidine-3-thiones(Vc)	5-o-Tolyl imino-1,2,4-triazolidine-3-thiones (VIc)	100
4-N-t-butyl-5-m-tolyl imino-1,2,4-triazolidine-3-thiones(Vd)	5-m-Tolyl imino-1,2,4-triazolidine-3-thiones (VId)	118
4-N-t-butyl-5-o-chloro phenyl imino-1,2,4-triazolidine-3-thiones(Ve)	5-o-Chloro phenyl imino-1,2,4-triazolidine-3-thiones (VIe)	178
4-N-t-butyl-5-p-chloro phenyl imino-1,2,4-triazolidine-3-thiones(Vf)	5-p-Chloro phenyl imino-1,2,4-triazolidine-3-thiones (VIf)	152

Note: All the compounds gave satisfactory C, H, N and S analysis

Conclusion

Triazole moiety and its various derivatives studied frequently in the past time and found potent in various pharmacological and pathological conditions. In the article the attempt to synthesize and characterize triazole derivatives were successfully carried out with elaborate characterization by spectral data. Obtained spectral data has prompted us to further evaluate the possible information from the spectra to understand synthetic approach and the dynamic property of molecules synthesized. These synthesized compounds are expected to possess biological activities.

Acknowledgement

The authors are grateful to the Principal, Shri Mungsaji Maharaj Mahavidyalaya, Darwha for allowing to carry out research work. The authors are also grateful to the Principal Dr. V. G. Thakare, Shri. Shivaji Science College, Amravati, for providing all essential laboratory facilities as well as to The Director , RSIC, Punjab University , Chandigrah for prviding elemental anlysis and IR,PMR, Mass Spectral data.

References

1. Hartwell J.L. and B.J. Abbot, In Advances in pharmacology and phemotherapy, 7th Edn, edited by Garrattini S., Goldin A., Hawking F., and I.J. Kopin. New York, Academic Press **(1969)**

2. Kubota S., Uda M. and Sato K., Synthesis and antimicrobial activity of 3-alkylthio- 5-pyridyl-1, 2, 4-triazoles and related compounds, *Chem. Pharm. Bull*., 26**(3),** 893-897 **(1978)**

3. Varma R.S., Green Chemical Synthesis and Process: edited by Anastas, P.T., Heine, L., and T. Williamson. *American Chemical Society*, Washington D.C**.,** In ASC Symposium Serial No.767 **(2000)**

4. Singh R.J. and Singh D.K., Syntheses characterization and biological activity of some 1, 2, 4-triazole derivatives, *E-J.Chem,* **6(3),**796-800 **(2009)**

5. Singh R. J. and Singh D. K., Syntheses, characterization and biological screening of some novel 1, 2, 4-triazoles, *Asian J. Research Chem,* **2(4),** 536-538 **(2009)**

6. Buscemi S., Vivona N. and Caronna T., *J. Org. Chem***.,** **61**, 8379 **(1996)**

7. Yoo B.R., Suk M.Y., Y-Man. Yu, S-Gyn. Hong and Jung I. N., *Bull. Korean Chem. Soc***.,** **19(3)**, 358 **(1998)**

8. Paulvannan K., Chen T. and Hale R., *Tetrahedron***,** **56**, 8071 **(2000)**
9. Vogel A.I., A Text Book of Practical Organic Chemistry, Including Qualitative Analysis, Longmans, **III**rd Ed**, (1958)**

10. Schmidte W., Striewsky M., Sectender and F. Hitzler , Leibig's Ann, 192, 568, **(1960)**

11. Dyson G.M. and Harington, *J. Chem. Soc.*,191**(1940**)

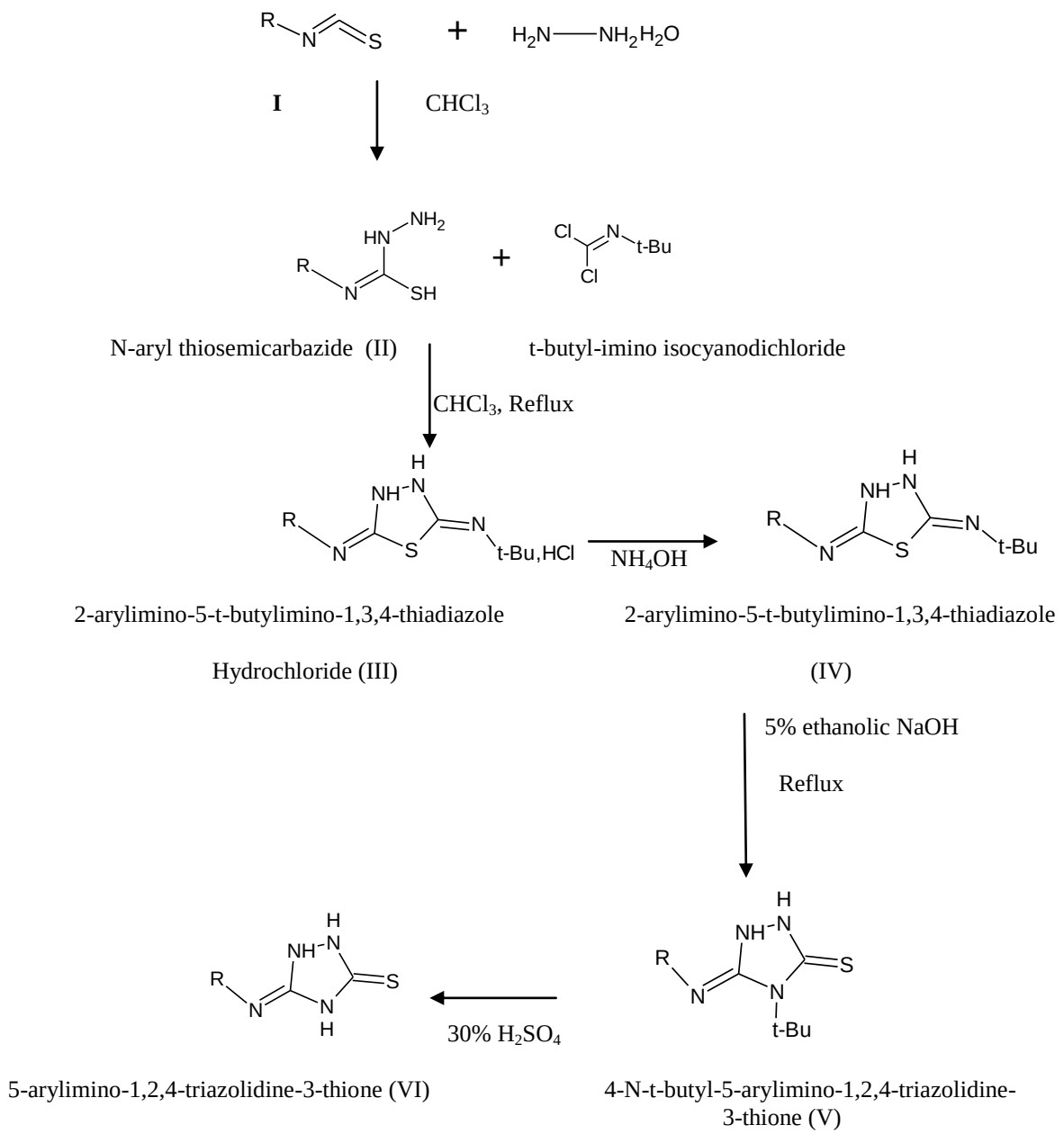
12. Bhaskar C.S., Vidhale N.N and Berad B.N, *Asian J.Chem*, 14,162 (**2002)**

13. Singh T., Bhattacharya A. and Verma V.K.*J. Indian Chem. Soc*., **69**,153-156,**(1992)**

14. Dyer J. R., Application of Absorption Spectroscopy of Organic Compound, Prentice-Hall **(1974)**

15. Lacey R. N., Structure and Mechanism of Organic Chemistry, *J. Chem. Soc.,* 1635 **(1960)**

SCHEME



Where R- (I, II, III, IV , V, VI)
a = p-tolyl, b = phenyl, c = o-tolyl, d = m-tolyl, e = o-chloro phenyl, f = p-chloro phenyl
Scheme. 1: - Scheme for synthesis of triazole derivatives