*Available online at* www.scholarsresearchlibrary.com

Scholars Research Library

**Archives of Applied Science Research, 2012, 4 (5):2110-2114**
*(http://scholarsresearchlibrary.com/archive.html)*

**ISSN 0975-508X**
**CODEN (USA) AASRC9**

# Synthesis, characterization and de-tert-butylation of 4-tert-butyl-5-aryl-2,4-dihydro-3*H*-1,2,4-triazole-3-thione

**[1]Rashidi N. A and [2]Berad B. N**

*[1]Post Graduate Department of Chemistry, Shri Shivaji Science College, Amravati (M.S) INDIA*
*[2]Department of Chemistry, RTM Nagpur University, Nagpur PINCode-440033, (M.S) INDIA*

---

## ABSTRACT

*Some new 4-tert-butyl-5-aryl-2,4-dihydro-3H-1,2,4-triazole-3-thione (IIIa-g) were synthesized from N-tert-butyl-2-aroyl thiosemicarbazide (N-tert-butyl-2-aroylhydrazine carbothioamide) (IIa-g). The later compounds (IIa-g) were prepared by the condensation of aromatic carboxylic acid hydrazides (Ia-g) and tert-butyl isothiocyanate. The compounds (IIa-g) on refluxing with 2N NaOH and ethanol and then on subsequent acidification with dilute glacial acetic acid furnished 4-tert-butyl-5-aryl-2,4-dihydro-3H-1,2,4-triazole-3-thione (IIIa-g). The title compounds were successfully de-tertbutylated into 5-aryl-2,4-dihydro-3H-1,2,4-triazole-3-thione (IVa-g). All the synthesized compounds were characterized by CHN analyses, IR, mass and 1H NMR spectral data.*

**Keywords:** Aromatic carboxylic acid hydrazides, tert-butyl isothiocyanate, hydrazine carbothioamide, dehydrative cyclisation, 1,2,4-triazole-3-thione.

---

## INTRODUCTION

1,2,4-triazole moiety constitute an important class of heterocyclic compounds with diverse biological activities, including antiparastic, analgesic, antibacterial and anti-inflammatory activities[1-2].Out of various substituted 1,2,4-triazole, the 4,5-disubstituted 1,2,4-triazole derivatives have gained a lot of interest due to their biological, industrial and agricultural importance. A well known example is of Flucanazole, a broad spectrum antifungal agent for treatment of superficial and systematic infections [3-4]. Some substituted mercaptotriazole have been reported to exhibit important pharmacological activity [5]. Acid hydrazides and thiosemicarbazide [6-8] have been in general use as the starting materials in some 1,2,4-triazole. In view of these observations, in the present study we have used acid hydrazide as one of the starting material and synthesized some new derivatives of substituted hydrazine carbothioamide. These hydrazine carbothioamide were used as the key intermediates for the synthesis of substituted 1,2,4-triazole. The base catalyzed dehydrative cyclisation of various hydrazine carbothioamide furnished corresponding 4,5-disubstituted 1,2,4-triazole-3-thione[8-12].

## MATERIALS AND METHODS

Melting point was determined by Thiele's tube method using liquid paraffin and was uncorrected. The purity of compounds was established by thin layer chromatography (TLC). Precoated silica gel aluminium plate 60F-254 (20 cm x 20 cm) with 250 µm thickness was used for TLC (E. Merck). Iodine was used to develop the TLC plates. Infrared (IR) spectra were recorded on a Shimadzu (Japan) 8400 S FT-IR spectrophotometer model using nujol and potassium bromide pellets ($\upsilon_{max}$ in cm-1). $^1$HNMR spectra were recorded on Brucker multinuclear FT NMR spectrometer model AV-400, 400 MHz using deuterated dimethylsulfoxide-containing tetramethylsilane (Me4Si) as internal standard (chemical shifts in δ ppm). The Mass spectrum was recorded on TOF MS ES+ Mass spectrometer.

Aromatic acid hydrazides were prepared by the reported procedure in literature [6-7]. Tert-butyl isothiocyanate was prepared by known procedure [13].

**Synthesis of N-tert-butyl-2-(4-nitro benzoyl) hydrazine carbothioamide (IIa)**
A mixture of 4-nitro benzohydrazide (0.01mol) and tert-butyl isothiocyanate (0.01mol) in ethanol (25.0 ml) was refluxed on a water bath for 2 hrs. The solvent was concentrated and the precipitated product was filtered, dried and recrystallized from ethanol, m.p $180^0$. Completion of reaction was monitored on TLC using silica gel-G coated plates by using ethyl acetate and petroleum ether (1:1) as the solvent and observed in U.V. light.

Other compounds **IIb-g** were prepared similarly and their physical data are recorded in Table 1
**IIa** IR[14,15] (KBr): 3329, 3278 (N-H), 3115(Ar-H), 2974, 2918,2850 (t-Bu-H),1682 (CONH), 1259 (C=S), 850 (p-substituted benzene).

**IIa** $^1$HNMR ($CDCl_3$): 1.4(s,9H,t-Bu), 4.4 (s,1H,N-H), 8.02-8.04 (d,2H,Ar-H), 8.09-8.11 (d,2H,Ar-H),8.1-8.2 (Sym dd,2H,N-H)

**Synthesis of N-tert-butyl-2-(aroyl) hydrazine carbothioamide (IIa)**
**Reagents: Aromatic acid hydrazide and tert-butyl isothiocyanate.**

| Aromatic acid Hydrazide (I) | N-tert-butyl-2-(aroyl) hydrazine carbothioamide (II) | % Yield | M.P $^0$C |
|---|---|---|---|
| 4-nitro bezohydrazide (Ia) | …..2-(4-nitro benzoyl) hydrazine carbothioamide (IIa) | 92% | 180 |
| Phenyl acetic acid hydrazide (Ib) | …..2-(phenylacetyl)hydrazine carbothioamide (IIb) | 78% | 109 |
| Benzohydrazide (Ic) | …..2-( benzoyl) hydrazine carbothioamide (IIc) | 85% | 140 |
| 2-hydroxy benzohydrazide (Id) | …..2-(2-hydroxy benzoyl) hydrazine carbothioamide (IId) | 88% | 159 |
| 2-chlorobenzo hydrazide (Ie) | …..2-(2-chloro benzoyl) hydrazine carbothioamide (IIe) | 76% | 130 |
| 4-chlorobenzo hydrazide (If) | …..2-(4-chloro benzoyl)hydrazine carbothioamide (IIf) | 83% | 152 |
| Isonicotinic acid hydrazide (Ig) | …..2-(isonicotinoyl)hydrazine carbothioamide (IIg) | 80% | 163 |

**Synthesis of 4-tert-butyl-5-(4-nitro phenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (IIIa).**
Compound **IIa** (0.01 mol) was added to ethanol (20 mL). To this NaOH (2N, 10 mL) was added which resulted in clear solution. It was refluxed for 1h and filtered. The filtrate was cooled and diluted with water, on acidification with dilute glacial acetic acid the required triazole was precipitated out. The mixture was kept aside for 1h, filtered, dried and recrystallised from ethanol, m.p $154^0$. Purity of the compound was checked by TLC using silica gel–G coated plates by using ethyl acetate: petro-ether (4:1) as solvent system, and observed under UV light.

Other compounds **IIIb-g** were prepared similarly and their physical data are recorded in Table 2

**IIIa** IR (KBr): 3329, 3277 (N-H), 2972,2919 (t-Bu-H),1528 (C=N), 1260 (C=S), 850 (p-substituted benzene)
**IIIa** 1HNMR (DMSO $d_6$): 1.4 (s, 9H, t-Bu), 8.0-8.1 (d, 2H, Ar-H), 8.2-8.2 (d, 2H, Ar-H) ,9.1 (s,1H, N-H). **M.S:** 279 ($M^+$+1), 263, 244, 233,118

**IIIb** IR (KBr): 3479, 3317 (N-H), 3161, 3086 (Ar-H), 2979, 2927, 2866 (t-Bu-H), 1662 (C=N), 1202(C=S). **IIIb** 1HNMR (DMSO $d_6$): 1,3-1.4 (s,9H,t-Bu),1.7 (s,2H,Ph-$CH_2$), 6.4 (s,1H,N-H), 6.9- 7.2 ( m, 5H, Ar-H).

**Synthesis of 4-tert-butyl-5-aryl-2,4-dihydro-3H-1,2,4-triazole-3-thione (III)**
**Reagents: N-tert-butyl-2-[(aryl) carbonyl] hydrazine carbothioamide and 2N NaOH**

| N-tert-butyl-2-(aroyl) hydrazine carbothioamide (II) | 4-tert-butyl-5-aryl-2,4-dihydro-3H-1,2,4-triazole-3-thione (III) | Yield % | M.P $^0$C | Mol.formula | % N Found (Calcd) |
|---|---|---|---|---|---|
| …..2-(4-nitro benzoyl) hydrazine carbothioamide (IIa) | …..-5-(4-nitro phenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (IIIa) | 85% | 154 | $C_{12}H_{14}N_4O_2S$ | 20.01 (20.13) |
| …..2-(phenylacetyl) hydrazine carbothioamide (IIb) | ….-5-benzyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (IIIb) | 71% | 112 | $C_{13}H_{17}N_3S$ | 16.86 (16.99) |
| …..2-( benzoyl) hydrazine carbothioamide (IIc) | …-5-phenyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (IIIc) | 78% | 132 | $C_{12}H_{15}N_3S$ | 17.98 (18.01) |
| …..2-(2-hydroxy benzoyl) hydrazine carbothioamide (IId) | …-5-(2-hydroxyphenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (IIId) | 80% | 136 | $C_{12}H_{15}N_3OS$ | 16.76 (16.85) |
| …..2-(2-chloro benzoyl) hydrazine carbothioamide (IIe) | …-5-(2-chloro phenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (IIIe) | 75% | 122 | $C_{12}H_{14}ClN_3S$ | 15.59 (15.69) |
| …..2-(4-chloro benzoyl)hydrazine carbothioamide (IIf) | …-5-(4-chloro phenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (IIIf) | 73% | 142 | $C_{12}H_{14}ClN_3S$ | 15.60 (15.69) |
| …..2-(isonicotinoyl) hydrazine carbothioamide (IIg) | …-5-(pyridin-4-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (IIIg) | 80% | 162 | $C_{11}H_{14}N_4S$ | 23.80 (23.91) |

**Synthesis of 5-aryl-2,4-dihydro-3H-1,2,4-triazole-3-thione (IVa)**

The product (IIIa) when subjected to hydrolysis by boiling with 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 (IVa), m.p 202$^0$C obtained was found to be successfully de-tert-butylated [16] from it's $^1$H-NMR data

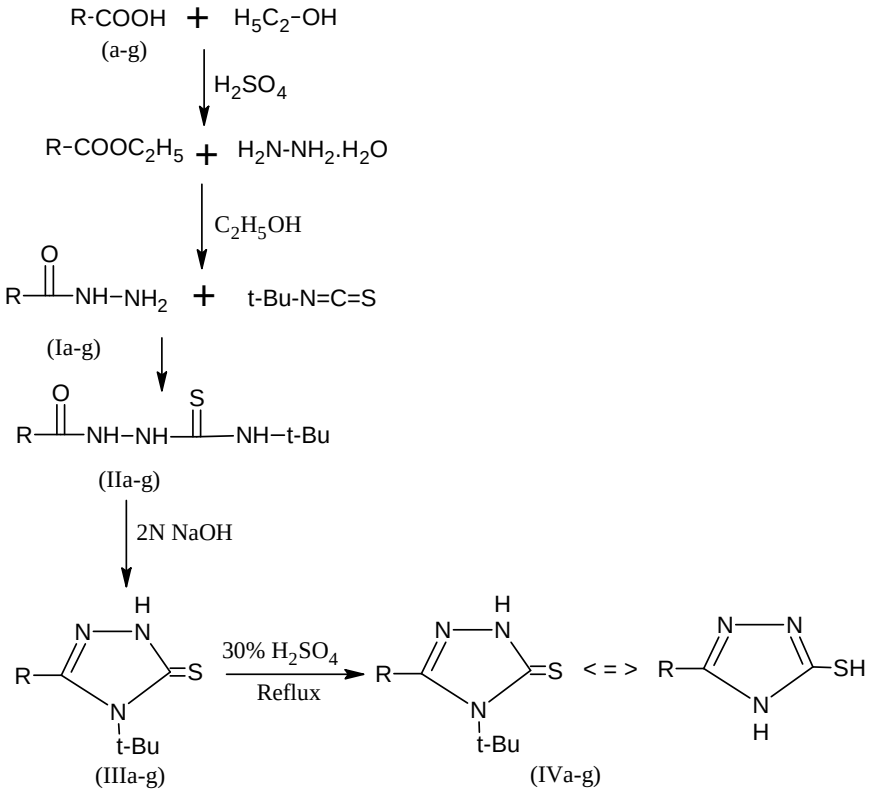
Other compounds **IVb-g** were prepared similarly and their physical data are recorded in Table.3

**IVa** 1HNMR (CDCl3): 7.6(s,1H,N-H) 8.0-8.1 (d,2H, Ar-H), 8.12-8.13 (d, 2H, Ar-H), 8.27(s,1H,N-H),.

**IVb** 1HNMR (CDCl3):1.2 (s,2H,-$CH_2$), 3.8 (s,1H,N-H), 7.1-7.2 ( m, 5H, Ar-H), 7.78 (s, 1H, N-H), 10.06 (s, 1H, N-H).

**Synthesis of 5-aryl-2,4-dihydro-3H-1,2,4-triazole-3-thione (IVa)**
**Reagents: 4-tert-butyl-5-aryl-2,4-dihydro-3H-1,2,4-triazole-3-thione (III) and 30% $H_2SO_4$.**

| 4-tert-butyl-5-aryl-2,4-dihydro-3H-1,2,4-triazole-3-thione (III) | 5-aryl-2,4-dihydro-3H-1,2,4-triazole-3-thione (IV) | Yield % | M.P $^0$C | Mol.formula | % N Found (Calcd) |
|---|---|---|---|---|---|
| …..-5-(4-nitro phenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (IIIa) | 5-(4-nitro phenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (IVa) | 46% | 245 | $C_8H_6N_4O_2S$ | 25.o6 (25.21) |
| ….-5-benzyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (IIIb) | 5-benzyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (IVb) | 32% | 165 | $C_9H_9N_3S$ | 21.88 (21.97) |
| …-5-phenyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (IIIc) | 5-phenyl-2,4-dihydro-3H-1,2,4-triazole-3-thione (IVc) | 39% | 202 | $C_8H_7N_3S$ | 23.65 (23.71) |
| …-5-(2-hydroxyphenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (IIId) | 5-(2-hydroxyphenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (IVd) | 41% | 210 | $C_8H_7N_3$ O S | 21.63 (21.75) |
| …-5-(2-chloro phenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (IIIe) | 5-(2-chloro phenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (IVe) | 33% | 178 | $C_8H_6ClN_3S$ | 19.65 (19.85) |
| …-5-(4-chloro phenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (IIIf) | 5-(4-chloro phenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (IVf) | 42% | 238 | $C_8H_6ClN_3S$ | 19.72 (19.85) |
| …-5-(pyridin-4-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (IIIg) | 5-(pyridin-4-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (IVg) | 28% | 218 | $C_7H_6N_4S$ | 22.90 (22.97) |




Where R= a = -$NO_2C_6H_4$, b = -$CH_2C_6H_5$, c = -$C_6H_5$, d = O-$OHC_6H_4$-,
e = O-$ClC_6H_4$-, f = P-$ClC_6H_4$-, g = -$C_5H_4N$

**Scheme (Fig 1 ): Synthesis of some 1,2,4-triazole derivatives**

**Mechanism of base catalysed de-hydrative cyclisation :**

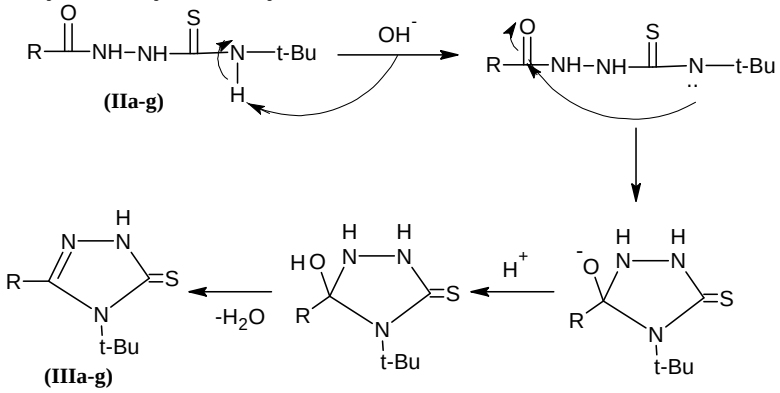



Fig 2: Mechanism of base catalysed dehydrative cyclisation
**of 1,4-disubstituted thiosemicarbazides**

## RESULTS AND DISCUSSION

The aromatic acid hydrazides were prepared by esterification of aromatic acid followed by treatment with hydrazine hydrate in absolute ethanol. In the present work thiosemicarbazides were used as the key intermediates for the synthesis of substituted 1,2,4-triazole. The condensation of 4-nitro benzohydrazide (Ia) with tert-butyl isothiocyanate was carried out on a water bath for 2 hrs. The solvent was concentrated and the precipitated product was filtered, dried and recrystallized from ethanol, m.p $180^0$. The structure of synthesized compound, N-tert-butyl-2-(4-nitro benzoyl) hydrazine carbothioamide (IIa) was confirmed on the basis of elemental, IRand $^1$H NMR data.
Other compounds **IIb-g** were prepared in similar fashion and related products were isolated in good yield **(Table 1).**

The N-tert-butyl-2-(4-nitro benzoyl) hydrazine carbothioamide (IIa) was refluxed with 2N NaOH in ethanol .A homogenous reaction mixture was obtained during the reaction process. The reaction mixture was cooled to room temperature and diluted with water on acidification with dilute acetic acid the product (IIIa) was precipitated out. It was filtered, washed thoroughly with cold water, dried and recrystallized from ethanol, m.p $154^0$. Purity of the compound was checked by TLC using silica gel–G coated plates by using ethyl acetate: petro-ether (4:1) as solvent system, and observed under UV light. On the basis of elemental analysis, IR , 1H NMR and Mass spectral data the compound (IIIa) has been assigned the structure of 4-tert-butyl-5-(4-nitro benzoyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (IIIa). It was found that during the reaction process the base catalyzed intramolecular dehydrative cyclization of the compound (IIa) furnished the corresponding 4-tert-butyl-5-(4-nitro benzoyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (IIIa) .

Other compounds **IIb-g** were prepared in similar fashion and related products were isolated in good yield **(Table 2).**

The hydrolysis of 4-tert-butyl-5-(4-nitro phenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (IIIa) with 30% sulphuric acid was carried out at refluxing temperature for 3 hr. The reaction mixture was poured in ice crushed water and the product (IVa) separated was purified by crystallization, m.p $202^0$C. The purity of the compounds was checked by TLC. The absence of signals due to H of t-butyl group in 1HNMR spectra confirmed that compound (IIIa) was successfully de-tert-butylated and converted to 5-(4-nitro phenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (IVa) .

Other compounds **(IVb-g)** were synthesized in good yield following the similar procedure **(Table 3).**

The synthetic route is outlined in *Scheme*. (Fig 1). The mechanism of base catalysed dehydrative cyclisation of 1,4-disubstituted thiosemicarbazide is given in (Fig 2).

## CONCLUSION

A series of new 4-tert-butyl-5-(aryl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (IIIa-g) were synthesized and successfully de-tert-butylated. The structures of all the synthesized compounds were in full agreement with the elemental analysis, $^1$H NMR and Mass spectral data. These synthesized compounds are expected to possess biological activities.

**Acknowledgement**
The authors are thankful to the Principal, Shri Mungsaji Maharaj Mahavidyalaya, Darwha for allowing to carry out research work. The authors are 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 , Chandigarh for providing elemental analysis, IR, PMR and Mass Spectral data.

## REFERENCES

[1] B Zech; H Croetz. *J. Indian chem. Soc*, **1981,** 280, 2923- 2926.
[2] X.P. Hui, C.H. Chu, Z.Y.Zang, Q.Wang and Q. Zhang, *Indian J Chem.*, **2002**, **41B**, 2176.
[3] K.W.Brammer et al., *Rev Infect Dis* **1990**; **12** (Suppl. 3): 318–26
[4] K.Richardson, *Curr. Med. Res. Opi*, **1991**, 12, 60.
[5] J.P.Lagorce, F.Comby, C.Raby, *Eur. J. Med. Chem*, **1992**. **27**, 359
[6] A.I.Vogel, A.R.Tatchell, B.S.Furnis, A.J.Hannaford, P.W.G.Smith, Vogel's Text Book of Practical Organic Chemistry, **5**th Ed. Singapore: Pearson Education; **2004**. p. 699**.**
[7] Sudeep K. Mandal et al., *International Journal of Pharma Sciences and Research (IJPSR)* Vol.1**(11), 2010**, 465-472
[8] K. Zamani et al., *Turk J Chem*. **27, 2003** , 119 - 125.
[9] A. Hussain K. Sharba , R. H. Al-Bayati, M. Aouad and N. Rezki, *Molecules* **2005**, ***10***, 1161-1168
[10] Sabir Hussain et al., *E-Journal of Chemistry*, **2008** Vol. 5, No.4, pp. 963-968.
[11] Milda M. Burbuliene, Vaida Sakociute, and Povilas Vainilavicius, *ARKIVOC.*, **2009 (xii)** 281-289.
[12] Alaa A. Hassan and Essmat M. El-Sheref, *Journal of Heterocyclic Chemistry*, **2010**, Vol **47**, 764-784.
[13] Schmidte, W. Striewsky, M. Sectender and F. Hitzler : Leibig's Ann, **1960**,192, 568,
[14] P.S.Kalsi, 'Spectroscopy of Organic Compounds', New Age International (P) Ltd., **Vth** edition, **2004**.
[15] W. Kemp, 'Organic Spectroscopy', Palgrave, **IIIth** edition, **2002**.
[16] Lacey R. N., Structure and Mechanism of Organic Chemistry, *J. Chem. Soc.*, **1960,**1635