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Research Article

SYNTHESIS, CHARACTERIZATION AND DE-TERTBUTYLATION OF 4-ARYLIMINO-3-TERT-BUTYL-1, 3, 4, 5-TETRAHYDRO-2H-1,3,5-BENZOTRIAZEPINE-2-THIONES

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ABSTRACT

Some new 4-aryl imino -3-tert-butyl-l,3,4,5-tetrahydro-2H-1,3,5-benzotriazepine-2 thione (Va-e) were synthesized via 2-aryl imino –N-4-tert-butylimino-4,5-dihydro-3,1,5- benzothiadiazepine (IVa-e) by the condensation of 1-(2-aminophenyl)-3-phenyl thioureas (IIa-e) with tert-butyl imino isocyanodichloride. The 1-(2-aminophenyl)-3-phenyl thioureas (IIa-e) were obtained by the treatment of o-phenylene diamine and aryl isothiocyanates. The synthesized compounds 4-aryl imino -3-tert-butyl-l,3,4,5-tetrahydro-2H-1,3,5-benzotriazepine-2-thione (Va-e) were successfully de-tertbutylated into respective 4-arylimino-1,3,4,5-tetrahydro-2H-1,3,5-benzotriazepine-2-thiones (VIa-e).

Keywords: 1, 3, 5-Benzotriazepine-2-thiones, 3,1,5 benzothiadiazepine, O-phenylene diamine, Aryl isothiocyanate, T-butyl imino isocyanodichloride.

INTRODUCTION

Literature studies showed that benzotriazepines have elicited extensive pharmacological interest and numerous derivatives[1-2] have been identified that display selective activities against a diverse array of biological targets[3]. Benzotriazepine comprises an interesting class of heteroaromatic compound because of their significant biological and pharmaceutical properties such as antibacterial, antiviral, psychotropic, antimalarial properties[4]. Although many methods for synthesizing benzothiadiazepine and benzotriazepine ring systems have been reported, they continue to receive a great deal attention. Much of the synthetic work in the benzotriazepine area has been stimulated by the remarkable range of psychotherapeutic activities of analogous benzodiazepines The present work describes the synthesis of 4-arylimino-3-t-butyl-1,3,4,5-tetrahydro-2H-1,3,5-benzotriazepine-2-thiones (Va-e) and their de-tert-butylation into respective 4-arylimino-1,3,4,5-tetrahydro-2H-1,3,5-benzotriazepine-2-thiones (VIa-e).

MATERIAL AND METHOD

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. Five substituted aryl isothiocyanate (Ia-e) were synthesized by the reaction of corresponding amines with carbon disulfide and ammonium hydroxide by following the reported method [5]. Tert-butyl isothiocyanate was prepared by Schmidte et al procedure[6] and t-butyl imino isocyanodichloride were prepared by the reported method[7].

Synthesis of 1-(2-aminophenyl)-3-o-tolyl thiourea (IIa)

The reaction of o-tolyl isothiocyanate and o-phenylenediamine were carried out in equimolar proportion in chloroform medium at reflux for 1.5 hr. After completion of reaction, distilled off solvent, product first washed with petroleum ether (60^0- 80^0) and then crystallized from ethanol, afforded off-white solid, m.p 162^0C. The product was soluble in organic solvent but insoluble in water and gave positive test for N and S elements.

The above reaction was extended to synthesize compounds (IIb-e)

(IIa) : **IR spectra**[8] : (KBr) cm-1 : 3433(NH), 3326 (NH), 3147-3017(Ar-H), 2971-2849(C-H, CH_3),1617 (C=N);

^{1}H-NMR (DMSOd6) ppm: 2.2(3H, s, CH_3), 3.2(2H,s,Ar-NH_2) 6.6-7.3 (10H, m, Ar-H), 8.5 (1H, s, NH), 8.8(1H, s, NH)

Synthesis of 4-o-tolylimino-N-4-(tert-butylimino)-4,5-dihydro-3,1,5-benzothiadiazepine (IVa)

The 1-(2-aminophenyl)-3-o-tolyl thiourea (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 purple coloured solid. It was crystallized from ethanol. The resultant solid was found to be mono hydrochloride (IIIa), m.p 98^0C. Basification of it with aqueous ammonia afforded a free base (IVa), crystallized from aqueous ethanol (70%), m.p 115^0C. 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 1-(2-aminophenyl)-3-aryl thiourea, the related 3,1,5-benzothiadiazepine (IVb-e) were isolated in good yield.

(**IVa**) : **IR spectra**: (KBr) cm-1: 3365 (NH), 3055(Ar-H), 2924 (C-H, CH_3), 1566 (C=N);

^{1}H-NMR (DMSOd6) ppm: 1.2-1.6 (9H, m, t-Bu), 2.2(3H, s, CH_3), 5.3(2H,broad,N-H) 6.8-7.2 (8H, m, Ar-H)

Synthesis of 4-o-tolylimino-3-t-butyl-1,3,4,5-tetrahydro-2H-1,3,5-benzotriazepine-2-thiones (Va)

The 4-o-tolylimino-N-4-(tert-butylimino)-4,5-dihy dro-3,1,5-benzothiadiazepine (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.p 91^0C. 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-e)

(Va) : IR spectra :(KBr) cm-1 : 3369 (N-H), 3058(Ar-H), 2925 (aliph-C-H), 1567(C=N), 1249(C=S); **(Va) ^{1}H-NMR** (DMSOd6) ppm : δ1.2-2.6(9H,m,t-Bu) 2.2 (3H, s, CH_3), 6.8-7.4 (8H, m, Ar-H) 7.7(1H, s, N-H), 8.1(1H,s,N-H); **(Va): Mass(m/z):** 338(M^+), 339(M^++1), 340(M^++2, diprotonated), 322, 281, 224, 106

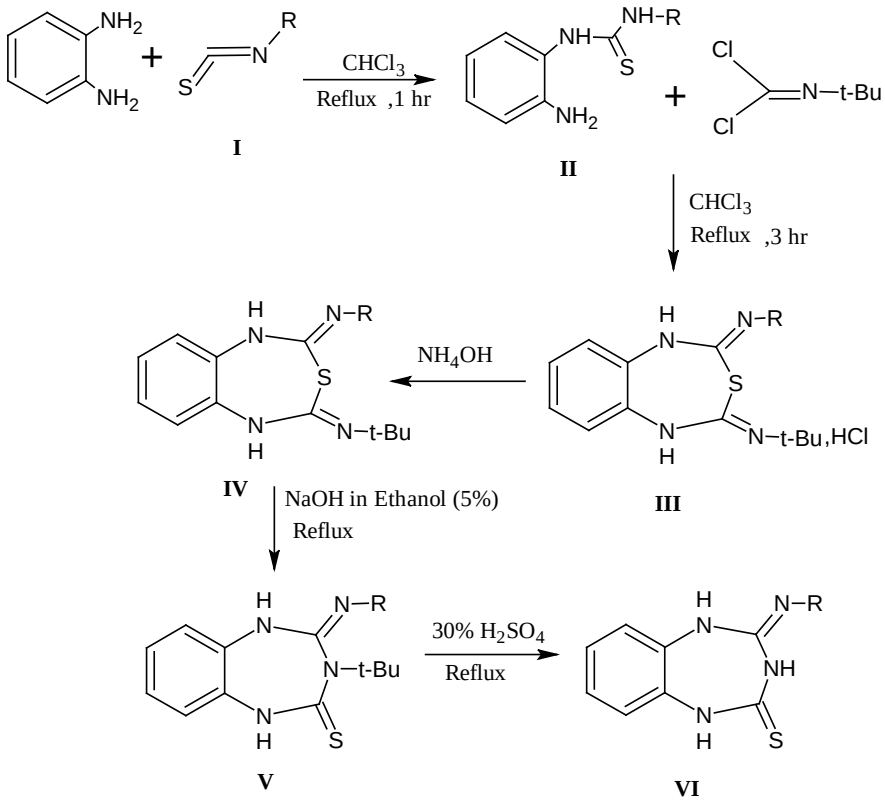
Synthesis of 4-o-tolylimino-1,3,4,5-tetrahydro-2H-1,3,5-benzotriazepine-2-thiones (VIa)

The product 4-o-tolylimino-3-t-butyl-1,3,4,5-tetrahydro-2H-1,3,5-benzotriazepine-2-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[9] (IVa), m.p 156^{0}C and gave positive test for N and S elements.

The above reaction was extended to synthesize compounds (VIb-e)

(VIa) : IR spectra :(KBr) cm-1 :3065(Ar-H),2918 (C-H, CH_3),1659(C=N),1117(C=S) **(VIa) : ^{1}H-NMR** (DMSOd6) ppm : δ 2.3 (3H, s, CH_3),3.4(2H,s,N-H) 7.1-7.3(8H, m, Ar-H) 7.9(br,s,N-H).

SCHEME



Where R= (I, II, III, IV, V, IV)

a = o-tolyl, b = phenyl, c = m-tolyl, d = p-tolyl,e = p-chlorophenyl

Fig 1 :Synthesis of benzotriazepine-2-thione derivatives

RESULTS AND DISCUSSION

The synthetic route is outlined in *Scheme.* (**Fig 1**)

Five substituted aryl isothiocyanate (Ia-e) were synthesized by the reaction of corresponding amines with carbon disulfide and ammonium hydroxide. The reaction of aryl isothiocyanate with o-phenylene diamine in chloroform medium were carried out at reflux for 1.5 hr. Cooling the reaction mixture and distilling off the solvent afforded a off-white solid. It was crystallized from ethanol. On the basis of physical characterization, elemental data and spectral analysis compound have been assigned the structure as 1-(2-aminophenyl)-3-aryl thiourea (IIa-e) **(Table 1).** The condensation of 1-(2-aminophenyl)-3-o-tolyl thiourea (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 purple coloured solid. It was crystallized from aqueous ethanol (70%), m.p 98^{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.p115^{0}C. On the basis of spectral data IR and 1H NMR and above facts the compound (IVa) has been assigned the structure as 4-o-tolylimino-N-4-(tert-butylimino)-4,5-dihydro-3,1,5-benzothiadiazepine (IVa) .

The other compounds (IVb-e) were prepared by extending the above reaction to other 1-(2-aminophenyl)-3-aryl thiourea (IIb-e) and the related 3,1,5- benzothiadiazepine (IVb-e) were isolated in good yield (**Table2).**

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-o-tolylimino-3-t-butyl-1,3,4,5-tetrahydro-2H-1,3,5-benzotriazepine-2-thiones (Va), m.p 91^0.The other compounds (Vb-e) were prepared by following the similar method (**Table 3**).

The resultant product (Va) was further converted into 4-o-tolylimino-1,3,4,5-tetrahydro-2H-1,3,5-benzotriazepine-2-thiones (VIa) by refluxing with 30% sulphuric acid underwent de-t-butylation. The structure of compound (VIa) was confirmed by 1H NMR spectral data. The 1H NMR spectra of compound (Va) showed a multiplet at 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 1H NMR spectra of product (VIa) confirmed that compound (Va) was successfully converted product (VIa), m.p 156^0 by de-t-butylation with 30% H_2SO_4.

The above reaction was extended to synthesize compounds (VIb-e) (**Table 3**)

The elemental analysis and spectral data IR, ^{1}H-NMR of all the synthesized compounds was in full agreement with the proposed structures.

PHYSICAL CHARACTERISATION

Table 1: Formation of 1-(2-aminophenyl)-3-aryl thiourea (II)

Reagent: o-phenylene diamine and aryl isothiocyanate (I)

Aryl isothiocyanate (I)	1-(2-aminophenyl)-3-aryl thiourea (II)	Yield %	M.P ^{0}C	N % found (calcd)
o-Tolyl isothiocyanate (Ia)	1-(2-aminophenyl)-3- o-tolyl thiourea (IIa)	86	162	16.02 (16.38)
phenyl isothiocyanate (Ib)	1-(2-aminophenyl)-3- phenyl thiourea (IIb)	73	149	17.13 (17.27)
m-Tolyl isothiocyanate (Ic)	1-(2-aminophenyl)-3-m-tolyl thiourea (IIc)	75	176	16.09 (16.38)
p-Tolyl isothiocyanate (Id)	1-(2-aminophenyl)-3-p-tolyl thiourea (IId)	85	152	16.11 (16.38)
p-chloro phenyl isothiocyanate (Ie)	1-(2-aminophenyl)-3-p-chloro phenyl thiourea (IIe)	89	159	15.02 (15.13)

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

Table 2: Formation of 4-arylimino-N-4-(tert-butylimino)-4,5-dihydro-3,1,5-benzothiadiazepine(IV)

Reagents: 1-(2-aminophenyl)-3-aryl thiourea (II) and t-butyl isocyanodichloride

1-(2-aminophenyl) -3-aryl thiourea (II)	4-arylimino-N-4-(tert-butylimino)-4,5-dihydro-3,1,5-benzothiadiazepine Hydrochloride(III)	Yield %	M.P ^{0}C	Eq. wt. Found (calcd)	4-arylimino-N-4-(tert-butyl imino)-4,5-dihydro-3,1,5-benzothiadiazepine (IV) (Free base).	M.P ^{0}C	N % Found (Calcd)
1-(2-amino phenyl)-3-o-tolyl thiourea(IIa)	4-o-Tolyl imino….-3,1,5-benzothiadiazepine Hydrochloride(IIIa)	83	98	370.22 (374.9)	4-o-Tolyl imino….3,1,5-benzothiadiazepine (IVa)	115	16.13 (16.55)
1-(2-amino phenyl)-3-phenyl thiourea (IIb)	4-Phenyl imino….-3,1,5-benzothiadiazepine Hydrochloride(IIIb)	74	92	358.2 (360.9)	4-Phenyl imino….3,1,5-benzothiadiazepine (IVb)	117	16.99 (17.27)
1-(2-amino phenyl)-3-m-tolyl thiourea (IIc)	4-m-Tolyl imino….-3,1,5-benzothiadiazepine Hydrochloride(IIIc)	76	102	369.87 (374.9)	4-m-Tolyl imino….3,1,5-benzothiadiazepine (IVc)	120	16.02 (16.55)
1-(2-amino phenyl)-3-p-tolyl thiourea (IId)	4-p-Tolyl imino….-3,1,5-benzothiadiazepine Hydrochloride(IIId)	88	106	370.9 (374.9)	4-p-Tolyl imino….3,1,5-benzothiadiazepine (IVd)	125	16.21 (16.55)
1-(2-amino phenyl)-3-p-chloro phenyl thiourea (IIe)	4-p-chloro phenyl imino….-3,1,5-benzothiadiazepine Hydrochloride(IIIe)	91	110	391.2 (395.3)	4-p-chloro phenyl imino….3,1,5-benzothiadiazepine (IVe)	128	15.11 (15.61)

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

Table 3: Formation of 4-arylimino-3-t-butyl-1,3,4,5-tetrahydro-2H-1,3,5-benzotriazepine-2-thiones(V)

Reagents: 4-arylimino-N-4-(tert-butylimino)-4,5-dihydro-3,1,5-benzothiadiazepine(IV)and NaOH in ethanol (5%).

4-arylimino-N-4-(tert-butylimino)-4,5-dihydro-3,1,5-benzothiadiazepine (IV) (Free base).	4-arylimino-3-t-butyl-1,3,4,5-tetrahydro-2H-1,3,5-benzotriazepine-2-thiones (V)	Yield %	M.P ^{0}C	N % Found (Calcd)	4-arylimino-1,3,4,5-tetrahydro-2H-1,3,5-benzotriazepine-2-thiones (VI)	M.P ^{0}C
4-o-Tolyl imino….3,1,5-benzothiadiazepine (IVa)	4-o-Tolyl imino….1,3,5-benzotriazepine-2-thiones (Va)	71	91	16.27 (16.55)	4-o-Tolyl imino….1,3,5-benzotriazepine-2-thiones (VIa)	156
4-Phenyl imino….3,1,5-benzothiadiazepine (IVb)	4-Phenyl imino….1,3,5-benzotriazepine-2-thiones (Vb)	62	100	17.02 (17.27)	4-Phenyl imino….1,3,5-benzotriazepine-2-thiones (VIb)	148
4-m-Tolyl imino….3,1,5-benzothiadiazepine (IVc)	4-m-Tolyl imino….1,3,5-benzotriazepine-2-thiones (Vc)	68	111	16.20 (16.55)	4-m-Tolyl imino….1,3,5-benzotriazepine-2-thiones (VIc)	161
4-p-Tolyl imino….3,1,5-benzothiadiazepine (IVd)	4-p-Tolyl imino….1,3,5-benzotriazepine-2-thiones (Vd)	79	105	16.23 (16.55)	4-p-Tolyl imino….1,3,5-benzotriazepine-2-thiones (VId)	172
4-p-chloro phenyl imino….3,1,5-benzothiadiazepine (IVe)	4-p-chloro phenyl imino….1,3,5-benzotriazepine-2-thiones (Ve)	82	116	15.40 (15.61)	4-p-chloro phenyl imino….1,3,5-benzotriazepine-2-thiones (VIe)	179

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

CONCLUSION

In conclusion, 1-(2-aminophenyl)-3-aryl thiourea (II**)** resulting from the aryl isothiocyanates and commercially available o-phenylenediamine constitute an interesting and efficient precursor for the synthesis of new 3,1,5-benzothiadiazepines and 1,3,5-benzotriazepine-2-thione systems which are condensed system of 1-(2-aminophenyl)-3-aryl thiourea (II) moiety with t-butyl imino isocyanodichloride. These products are expected to possess biological activities.

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