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Application of N-tert-butyl Isocyanodichloride in the Synthesis of New Derivatives of 1,3,4-Thiadiazolidines

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Abstract: *N-tert-butyl isocyanodichlorides is one of the important reagents in the synthesis of nitrogen containing acyclic and heterocyclic compounds. N-tert-butyl isocyanodichlorides undergo nucleophilic substitution reactions involving the displacement of both the chlorine atoms and can be potentially useful in the synthesis of various different 5, 6 and 7 membered acyclic and heterocyclic compounds. Synthetic chemistry of N-aryl and alkyl isocyanodichloride with special reference to their utility as intermediates in the synthesis of nitrogen containing 5- membered heterocyclic compounds is explored here. The condensation reaction of N-tert-butyl isocyanodichloride with different substituted N-aryl thiosemicarbazide resulted in the synthesis of various different substituted 1,3,4-thiadiazolidine. In the present work attempts have been made to use N-tert-butyl isocyanodichloride in the synthesis of 5-membered heterocyclic compounds 1,3,4-thiadiazolidines namely 2-N-t-butylimino-3-γ-picolinoyl-5-p-arylimino-1,3,4-thadiazoles (IVa) and 2-arylimino-5-t-butylimino-1,3,4-thiadiazolidine (IVA) with different substituent and some by incorporating isoniazide in it's structure in view of having more promising pharmacological and pathological activities. The structures of the synthesized compounds were established on the basis of chemical properties, IR and NMR spectral data. These compounds are expected to possess biological activities.*

Keywords: Substituted 1,3,4-thiadiazolidine, N-aryl thiosemicarbazide, tert-butyl isocyanodichloride, cyclo condensation

I. INTRODUCTION

1,3,4-thiadiazoles and derivatives have been widely studied for analytical and industrial interest [1], [2], [3]. Different approaches have been reported for the preparation of 1,3,4-thiadiazoles and it's derivative. Literature Survey reveals that synthetic chemistry of N-aryl and alkyl isocyanodichloride [4], [5], [6], [7] with special reference to their utility as intermediates in the synthesis of nitrogen containing heterocyclic compounds. It appeared quite interesting to explore their synthetic applications towards the nitrogen containing 5and 7- membered acyclic and heterocyclic compounds. The present paper mainly focus on the synthetic application of N-tert-butyl isocyanodichloride in the synthesis of 5-membered heterocyclic compounds such as 2-N-t-butylimino-3-γ-picolinoyl-5-p-arylimino-1,3,4-thadiazoles (IVa) and 2-arylimino-5-t-butylimino-1,3,4-thiadiazolidine (IVA).

II. EXPERIMENTAL

All melting points were measured using electro-thermal apparatus are uncorrected. IR spectra were measured using KBr disc plate technique on a Bruker FT-IR spectrophotometer. ^{1}HNMR spectra (DMSO-d_6 and $CDCl_3$) were carried out on a Bruker Advance 400 MHz spectrometer using TMS as internal reference (chemical shifts in ó, ppm).The reagent required for the synthesis of 1,3,4-thiadiazolidines are Isoniazide, aryl isothiocyanates [8] and tert-butyl isothiocyanate [9]. The tert-butylimino isocyanodichloride was prepared following earlier reported method [10]. The 1-γ-picolinoyl-4-aryl-3-thiosemicarbazides [11] (IIa-f) were prepared by the reaction of Isoniazide and aryl isothiocyanate (Ia-f) in chloroform medium as below

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2.1 Preparation of 1-γ-picolinoyl-4-p-tolyl-3-thiosemicarbazides (IIa)

Isoniazide and p-tolyl isothiocyanate (Ia) was reacted in chloroform medium for 1.5 h. On removal of chloroform by vacuum distillation a colourless solid (IIa) was separated. It was washed with petroleum ether (60-80^0) and crystallized from ethanol, m.p 164^{0}C having molecular formula $C_{14}H_{14}N_4OS$.

(**IIa**): **IR spectra**: (KBr) cm-1: 3271,3232 (N-H), 1668 (C=O), 1310 (C-N), 1254 (C=S); **1H-NMR** (DMSOd^6) ppm: 2.2 (3H, s, Ar-CH3), 3.66 (1H, s, N-H), 8.6-8.62 (1H,d, NH-NH), 8.65-8.67 (1H,d, NH-NH), 7.04-7.07 (2H, d, Ar-H), 7.2-7.3(2H, d, Ar-H), 7.6-7.7 (2H, d, Pyridyl-H), 7.8-7.81 (2H, d, Pyridyl-H).

On the basis of above chemical properties and IR and NMR spectral data [12], [13], [14], the compound (IIa) has been assigned the structure, 1-γ-picolinoyl-4-p-Tolyl-3-thiosemicarbazide (IIa). The reaction of isoniazide was capable of extension to different aryl isothiocyanates (Ib-f), and the related products have been isolated in good yield. (Table -1)

2.2 Preparation of 2-N-t-butylimino-3-γ-picolinoyl-5-p-tolylimino-1,3,4-thiadiazoles (IVa)

1-γ-picolinoyl-4-p-tolyl-3-thiosemicarbazide (IIa) (0.01) suspended in chloroform (15.0 ml) was refluxed over water bath for 3.0 hr with N-t-butyl imino isocyanodichloride (0.01 mole). After completion of reaction, the reaction mixture was cooled and product was recovered with petroleum ether (60-80°C) followed by addition of ethanol; a solid acidic to litmus was identified as monohydrochloride of 2-N-t-butylimino-3-γ-picolinoyl-5-p-tolylimino-1,3,4-thiadiazole (IIIa), yield 85%, m.p. 178°C. On basification and crystallization from ethanol, m.p. 218°C having molecular formula $C_{19}H_{21}N_5OS$. The compound gave positive test for N and S elements and found to be non-desulphurizable when boiled wit alkaline plumbite solution.

(**IIIa**): **IR spectra**: (KBr) cm-1: 3313 (N-H), 1618 (C=O), 1573 (C=N), 1298 (C-N), 697 (C=S); **1H-NMR** (DMSOd^6) ppm: 1.2 (9H, s, t-Bu-H), 2.2 (3H, s, Ar-CH3), 7.0 (2H, d, Ar-H), 7.5 (2H, d, Ar-H), 7.7 (2H, d, Pyridyl-H), 7.9 (2H, d, Pyridyl-H), 8.7 (1H, s, N-H).

On the basis of above chemical properties and spectral data, the compound (IVa) has been assigned the structure, 2-N-t-butylimino-3-γ-picolinoyl-5-p-tolylimino-1,3,4-thiadiazoles (IVa). The other compounds (IVb-f) were prepared by extending the above reaction to other, 1-γ-picolinoyl-4-aryl-3-thiosemicarbazides (IIb-f) and the related products were isolated in good yield. (Table-1)

2.3 Preparation of N-p-tolyl thiosemicarbazide (IIA)

The N-p-tolyl thiosemicarbazide (IIA) was prepared by earlier reported method**.**

The product (IIA) was recrystallized from ethanol, yield 76% ,m.p 158 ^{0}C.

(**IIA**) : **IR spectra**: (KBr) cm-1: 3296 (NH), 1619 (C=N), 1275 (C-N), 1178(C=S); **1H-NMR** (DMSOd6) ppm: 2.2(3H, s, Ar-CH3), 4.2 (2H, bs, N-H) 7.2-7.06 (2H, d, Ar-H), 7.03-7.37 (2H, d, Ar-H), 8.6(1H, s, N-H) .

The other **N-**Aryl thiosemicarbazide (IIB-F) were prepared by similar method using different aryl isothiocyanates (IA-F).

2.4 Preparation of 2-p-tolylimino-5-t-butylimino-1,3,4-thiadiazolidine (IVA)

N-p-tolyl thiosemicarbazide (IIa) (0.01 mole) was refluxed with tert-butyl isocyanodichloride (0.01 mole) in chloroform medium over water bath for 3.0 hr. The evolution of hydrogen chloride gas was clearly noticed. On cooling, distilling off chloroform and on washing repeatedly with petroleum ether (60-80°C) gave a granular solid, crystallised from ethanol. It was acidic to litmus and on determination of equivalent weight, it was found to be a monohydrochloride (IIIA), yield 78%, m.p. 72-74°C. It, on basification with dilute ammonium hydroxide solution afforded a free base, (IVA). It was crystallised from ethanol, m.p. 102°C.The compound was insoluble in water but soluble in organic solvents and found to be non-desulphurizable when boiled with alkaline lead acetate solution.

molecular formula was found to be $C_{13}H_{18}N_4S$.

(**IVA**) : **IR spectra**: (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: 1.2-1.4 (9H, m, t-Bu), 2.1(3H, s, CH3) 6.92-7.2 (4H, m, Ar-H), 7.3 (1H, d, NH), 7.4(1H, d, NH)

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(**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, CH3) 6.92-7.2 (4H, m, Ar-H), 7.4 (1H, d, NH), 8.4(1H, d, NH).

On the basis of chemical properties and spectral data, the compound (IVA) has been assigned the structure, 2-p-tolylimino-5-t-butylimino-1,3,4-thiadiazolidine (IVA). On extending the above reaction to other **N**-Aryl thiosemicarbazide (IIB-F), the related products were isolated in good yield. (Table-1)

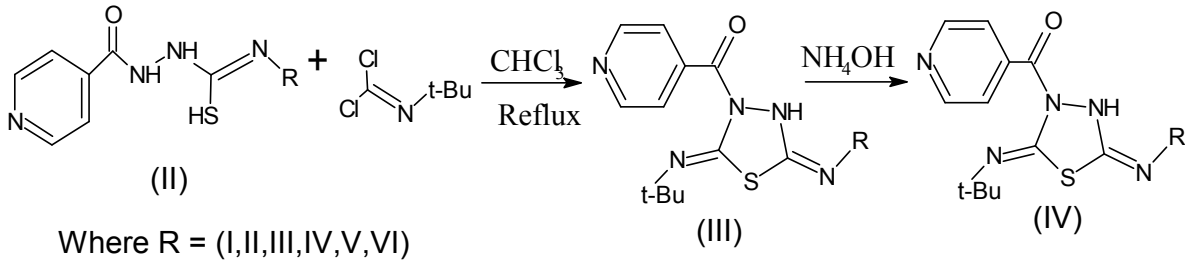
III. Results and Discussion

The 1-γ-picolinoyl-4-p-tolyl-3-thiosemicarbazides (IIa) were prepared by the reaction between Isoniazide and different p-tolyl isothiocyanate (Ia) in chloroform medium. Further the cyclo-condensation of 1-γ-picolinoyl-4-p-tolyl-3-thiosemicarbazides (IIa) with t-butyl imino isocyanodichloride in chloroform lead to the light yellow coloured solid with the evolution of hydrogen chloride gas. The product was acid to litmus. On basification with ammonium hydroxide, afforded a free base (IVa)) crystallized from aqueous ethanol, m.p. 218°C. On the basis of spectral data IR and 1H NMR and above facts the compound (IVa) has been assigned the structure as 2-N-t-butylimino-3-γ-picolinoyl-5-p-tolylimino-1,3,4-thiadiazoles (IVa).

The other (IVb-f) were prepared by similar method and the related products were isolated in good yield. (Table-1). The N-p-tolyl thiosemicarbazide (IIA) was prepared by the treatment of p-tolyl isothiocyanate(Ia) with hydrazine hydrate in chloroform medium. The product (IIA) was recrystallized from ethanol, yield 76% ,m.p 158 ^{0}C.

The condensation of N-p-tolyl thiosemicarbazide (IIA) with tert-butyl isocyanodichloride was carried out for 3.0 hr. The evolution of hydrogen chloride gas was clearly noticed. On cooling and distilling off chloroform, the product was acidic and found to be a monohydrochloride (IIIA) which on basification with dilute ammonium hydroxide solution afforded a free base (IVA), crystallised from ethanol, m.p. 102°C. The structure of the synthesized compounds were confirmed by elemental analysis and spectral data IR, 1H-NMR and Mass of all the synthesized compounds was in full agreement with the proposed structures. The formation of compounds II, III and IV can be explained by the following ***reaction scheme1****and* ***reaction scheme2***.

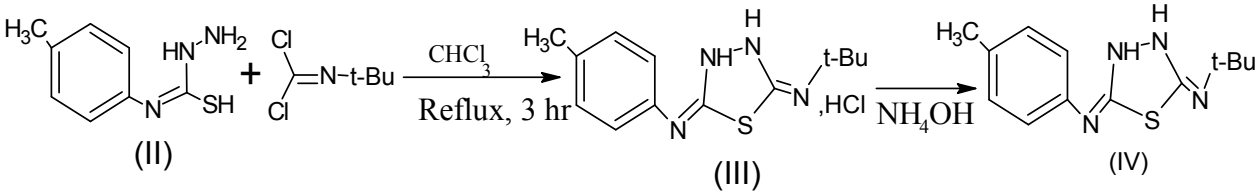
Reaction 1



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

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

Reaction 2



Where R= (II, III, IV)

A= p-tolyl, B=o- tolyl, C = m-tolyl,D= phenyl,
E=o-chlorophenyl, F= p-chlorophenyl

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IV. CONCLUSION

The present work attempt to synthesize some new derivatives of 1,3,4-thiadiazolidines namely 2-N-t-butylimino-3-γ-picolinoyl-5-p-arylimino-1,3,4-thadiazoles (IVa) and 2-arylimino-5-t-butylimino-1,3,4-thiadiazolidine (IVA) with different substituent and some by incorporating isoniazide in it's structure in view of having more promising pharmacological and pathological activities. The structures of the synthesized compounds were established on the basis of chemical properties and IR and NMR spectral data. These compounds are expected to show antimicrobial properties. These synthesized compounds are expected to possess biological activities.

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Table: Formation of 2-N-t-butylimino-3-γ-picolinoyl-5-Arylimino-1,3,4-thiadiazoles (IV) And Formation of 2-arylimino- 5-N-t-butylimino-1,3,4-thiadiazolidine (IV).

1- γ-picolinoyl-4-aryl-3-thio semicarbazides (II)	M.P ^{0}C	2-N-t-butylimino-3-γ-picolinoyl-5-arylimino-1,3,4-thiadiazole(free base) (IV)	M.P ^{0}C	Aryl thiosemicarbazide (II)	M.P ^{0}C	2-aryl imino- 5-N-t-butylimino-1,3,4-thiadiazolidine (IV) (Free base)	M.P ^{0}C
$C_{14}H_{14}N_4OS$ (IIa)	164	$C_{19}H_{21}N_5OS$ (IVa)	218	$C_8H_{11}N_3S$ IIA	158	$C_{13}H_{18}N_4S$ IVA	102
$C_{14}H_{14}N_4OS$ (IIb)	170	$C_{19}H_{21}N_5OS$ (IVb)	263	$C_8H_{11}N_3S$ IIB	130	$C_{13}H_{18}N_4S$ IVB	144
$C_{14}H_{14}N_4OS$ (IIc)	184	$C_{19}H_{21}N_5OS$ (IVc)	251	$C_8H_{11}N_3S$ IIC	140	$C_{13}H_{18}N_4S$ IVC	115
$C_{13}H_{12}N_4OS$ (IId)	194	$C_{18}H_{19}N_5OS$ (IVd)	224	$C_7H_9N_3S$ IID	105	$C_{12}H_{16}N_4S$ IVD	164
$C_{13}H_{11}ClN_4OS$ (IIe)	162	$C_{18}H_{18}ClN_5OS$ (IVe)	242	$C_7H_8N_3ClS$ IIE	120	$C_{12}H_{15}N_4SCl$ IVE	110
$C_{13}H_{11}ClN_4OS$ (IIf)	186	$C_{18}H_{18}ClN_5OS$ (IVf)	231	$C_7H_8N_3ClS$ IIF	165	$C_{12}H_{15}N_4SCl$ IVF	156