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Research Article

CYCLO-CONDENSATION OF SUBSTITUTED THIOSEMICARBAZIDES: SYNTHESIS OF 2,5- DISUBSTITUTED 1,2,4-TRIAZOLIDIN- 3-THIONE

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A B S T R A C T

2-N-t-butylimino-3-γ-picolinoyl-5-arylimino-1,3,4-thiadiazoles (IVa-f) have been synthesized following the interaction of 1-γ-picolinoyl-4-aryl-3-thiosemicarbazides (IIIa-f) and t-butyl imino isocyanodichloride. The former (IIIa-f) in turn have been prepared by the condensation of aryl isothiocyanates (Ia-f) and isoniazide. The intermediate products (IVa-f) have been first isomerized into 2-γ-picolinoyl-4-N-t-butyl-5-arylimino-1,2,4-triazolidine-3-thiones (Va-f). The product (Va-f) have been successfully de-t-butylated into respective 2- γ-picolinoyl-5-arylimino-1,2,4-triazolidine-3-thiones (VIa-f). The structures of these compounds were established on the basis of elemental analysis and IR, PMR, Mass spectral data.

INTRODUCTION

From a last decade a lot of work is going on, on the triazole ring, scientists develop a lot of new compounds related to this moiety and screened them for their different pharmacological activities to get a molecule which have good pharmacological activity and lesser side effect. Synthesis of various substituted 1,3,4-thiadiazole and 1,2,4-triazole are reported in the literature. 1,2,4-Triazoles show various biological activities (Singh R. J. and Singh D. K. 2009; Upmanyu N. 2006) and have been synthesized from different compounds (Bhaskar C.S.2002; Buscemi S.1996; Yoo B. R. 1998). Most of them possess good pharmacological activity. Isoniazide is itself a potent drug; therefore we incorporated some part of it as a substituent in the synthesis of some new derivative of triazole. The current work describes the synthesis of 2-γ-picolinoyl-4-N-t-butyl-5-arylimino-1,2,4-triazolidine-3-thiones (Va-f) and their de-t-butylation into respective 1,2,4-triazolidine-3-thiones (VIa-f).

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 (Vogel A. I. 1958) and tert-butyl isothiocyanate (Striewsky W. 1960). The tert-butylimino isocyanodichloride was prepared following earlier reported method (Dyson G. M. and Harington. 1940). The 1-γ-picolinoyl-4-aryl-3-thiosemicarbazides (IIa-f) were prepared by the reaction of Isoniazide and aryl isothiocyanate (Ia-f) in chloroform medium as below

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

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 $C_{14}H_{14}N_4OS$.

(IIIa): IR spectra: (KBr) cm-1: 3271,3232 (N-H), 1668 (C=O), 1310 (C-N), 1254 (C=S); 1H-NMR (DMSOd6) 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 (Singh. T., Bhattacharya A. and Verma V.K. 1992; Dyer J. R.1974; Colthup N. B., Daly L. H. and Wiberly S. E.1964), 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)

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Interaction of 1-γ-picolinoyl-4-aryl-3-thiosemicarbazides (II) and N-t-butyl imino isocyanodichloride:

Synthesis of 2-N-t-butylimino-3-γ-picolinoyl-5-arylimino-1,3,4-thiadiazoles (IV):

Experiment No. 1

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 mole) was suspended in chloroform (15.0 ml). To this a solution of N-t-butyl imino isocyanodichloride (0.01 mole) in chloroform was added. The reaction mixture was refluxed over water bath for 3.0 hr. The evolution of hydrogen chloride gas was observed. After completion of reaction, the reaction mixture was cooled and chloroform was distilled off, when a sticky mass was obtained. It was repeatedly washed with petroleum ether (60-80°C) followed by addition of ethanol; a solid acidic to litmus was isolated. It was crystallised from ethanol, and 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 with dilute ammonium hydroxide solution afforded a free base (IVa). It was crystallised from ethanol, m.p. 218°C having molecular formula C19H21N5OS. 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-2.2)

Preparation of 2-γ-picolinoyl-4-N-t-butyl-5-p-tolyl imino-1,2,4-triazolidin-3-thione (Va) (Isomerization)

The 2-N-t-butylimino-3-γ-picolinoyl-5-p-tolylimino-1,3,4-thiadiazoles (IVa) (0.01 mole) was refluxed with 5% ethanolic NaOH (15 ml) for 1.5 hr. After completion of reaction, the reaction mixture was cooled and poured in ice crushed water. The greenish yellow solid was obtained. It was crystallized from ethanol, yield 83%, m.p 226-228^{0}C having molecular formula $C_{19}H_{21}N_5OS$.

(**IIIa**): **IR spectra**: (KBr) cm-1: 3232 (N-H), 1619 (C=O), 1546 (C=N), 1297 (C=S);

^{1}H-NMR ($DMSOd^6$) ppm: 1.2 (9H, s, t-Bu-H), 2.4 (3H, s, Ar-CH3), 7.1-7.3 (4H, m, Ar-H), 7.7-7.8 (4H, m, Pyridyl-H), 8.4 (1H, s, N-H). **MS (m/z) :**[M^+] peak at m/z 367 and 366 [M^+-1], 351, 275, 223 and 106 which confirmed its molecular weight and possible fragmentation.

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

De-t-butylation of 2-γ-picolinoyl -4-N-t- butyl-5-aryl imino-1,2,4-triazolidin-3-thiones (V).

Preparation of 2- γ-picolinoyl-5-p-tolylimino-1,2,4-triazolidin-3-thione (VIa).

The 2-γ-picolinoyl-4-N-t-butyl-5-p-tolyl imino-1,2,4-triazolidin-3-thione (Va) (2 gm) was hydrolyzed by boiling with 30% sulphuric acid (10 ml) under reflux for 3.0 h underwent de-tert-butylation (Lacey R. N.1960). The solid gradually went into solution and a clear solution was obtained. After completion of reaction, the product (VIa) poured in ice crushed water. It was crystallized, m.p 142^{0}C having molecular formula $C_{15}H_{13}N_5OS$.

^{1}H-NMR ($DMSOd^6$) ppm: 2.4 (3H, s, Ar-CH3), 7.1-7.3 (4H, m, Ar-H), 7.7-7.8 (4H, m, Pyridyl-H), 8.4 (1H, s, N-H) 8.7 (1H, s, N-H).

The absence of signal for t-Bu proton in PMR spectra of compound (VIa) proved that compound (Va) was successfully de-tert-butylated. On the basis of above chemical properties and spectral data, the compound (VIa) has been assigned the structure, 2-γ-picolinoyl-5-p-tolyl imino-1,2,4-triazolidine-3-thione (VIa). The other compounds (VIb-f) were prepared by extending the above reaction to other, 2-γ-picolinoyl-4-N-t-butyl-5-aryl imino-1,2,4-triazolidine-3-thiones (Vb-f) and the related products were isolated in good yield. (Table-2).

Table 1 Formation of 1-γ-picolinoyl-4-aryl-3-thiosemicarbazides (II)

Reagents : Isoniazide and Aryl isothiocyanates (I)

Aryl isothiocyanate (I)	1-γ-picolinoyl-4-Aryl-3-thiosemicarbazides (II)	Yield %	M.P ^{0}C	Found (Calculated) %			
				C%	H%	N%	S%
	1-γ-picolinoyl-4-p-tolyl-3-thiosemicarbazide (IIa)						
	1-γ-picolinoyl-4-o-tolyl-3-thiosemicarbazide (IIb)						
p-tolyl isothiocyanate (Ia)		87	164	58.73 (58.74)	4.62 (4.89)	19.46 (19.57)	11.01 (11.19)
o-tolyl isothiocyanate(Ib)	1-γ-picolinoyl-4-m-tolyl-thiosemicarbazide (IIc)	91	170	58.65 (58.74)	4.80 (4.89)	19.40 (19.57)	11.23 (11.19)
m-tolyl isothiocyanate(Ic)		91	184	58.60 (58.74)	4.82 (4.89)	19.50 (19.57)	10.94 (11.19)
phenyl isothiocyanate(Id)	1-γ-picolinoyl-4-phenyl-3-thiosemicarbazide (IId)	85	194	57.15 (57.35)	4.39 (4.41)	20.40 (20.58)	11.85 (11.75)
o-chlorophenyl isothiocyanate(Ie)		75	162	50.72 (50.90)	3.39 (3.59)	18.00 (18.27)	10.29 (10.44)
p-chlorophenyl isothiocyanate(If)	1-γ-picolinoyl-4-o-chlorophenyl-3-thiosemicarbazide (IIe)	83	186	50.70 (50.90)	3.46 (3.59)	18.05 (18.27)	10.27 (10.44)
	1-γ-picolinoyl-4-p-chlorophenyl-3-thiosemicarbazide (IIf)						

Table 2 Synthesis of 2-N-t-butylimino-3-γ-picolinoyl-5-Arylimino-1,3,4-thiadiazoles (IV):Isomerisation of (IV) & De-tert-bultylation into 2-γ-picolinoyl-5-arylimino-1,2,4-triazolidin-3-thione (VI)

Reagents : 1-γ-picolinoyl-4-Aryl-3-thiosemicarbazides (II) and t-butyl isocyanodichloride

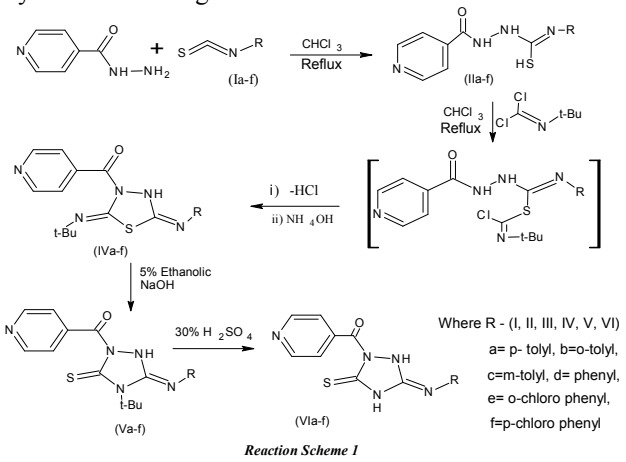
1-γ-picolinoyl-4-aryl-3-thio semicarba zides (II)	2-N-t-butylimino-3-γ-picolinoyl-5-arylimino-1,3,4-thiadiazole(free base)(IV)	M.P °C	2-γ-picolinoyl-4-N-t-butyl-5-arylimino-1,2,4-triazolidine-3-thione (V)	Yield %	M.P °C	2-γ-picolinoyl-5-arylimino-1,2,4-triazolidine-3-thione (VI)	M.P °C	Mol. formula
(IIa).	(VIa)	218	(Va)		226-228	(VIa)	123	
(IIb).	(VIb)	263	(Vb)	87	152-154	(VIb)	106	
(IIc).	(VIc)	251	(Vc)	91 93	201-203	(VIc)	118	$C_{15}H_{13}N_5OS$ $C_{15}H_{13}N_5OS$ $C_{15}H_{13}N_5OS$
(IIId).	(VId)	224	(Vd)	83	210-212	(VId)	134	$C_{14}H_{13}N_5OS$ $C_{14}H_{12}ClN_5OS$
(IIIe).	(VIe)	242	(Ve)	78 81	158-160	(VIe)	178	$C_{14}H_{12}ClN_5OS$
(IIIf).	(VIf)	231	(Vf)		262-264	(VIf)	152	

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 determination of equivalent weight it was found to be mono hydrochloride (IIIa-f) yield 85%, m.p. 178°C.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 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-2). Isomerisation of product (IVa) was carried out by refluxing with 5% ethanolic NaOH for 1.5 hr.On the basis of elemental data and spectral analysis the structure of isomerised product (Va) was found to be 2-γ-picolinoyl-4-N-t-butyl-5-p-tolyl imino-1,2,4-triazolidine-3-thione. The other compounds (Vb-f) were prepared by extending the above reaction to other, 2-N-t-butylimino-3-γ-picolinoyl-5-p-tolylimino-1,3,4-thiadiazoles (IVb-f) and the related products were isolated in good yield. (Table-2).

The 2-γ-picolinoyl-4-N-t-butyl-5-p-tolyl imino-1,2,4-triazolidin-3-thione (Va) was hydrolyzed by boiling with 30% sulphuric acid under reflux for 3.0 h. underwent de-t-butylation. The structure of 2 -γ-picolinoyl-5-p-tolyl imino-1,2,4-triazolidine-3-thione (VIa) was confirmed from it's ^{1}H NMR spectral data. 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 de-tertbutylated into 2-γ-picolinoyl-5-p-tolyl imino-1,2,4-triazolidine-3-thione (VIa). The above reaction was extended to synthesize compounds (VIb-f) (Table 2). The 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, IV, V and VI can be explained by the following ***reaction scheme1***.



Reaction Scheme 1

CONCLUSION

The present work attempt to synthesize some new derivatives of triazole moiety by incorporating isoniazide in it's structure in view of having more promising pharmacological and pathological activities and confirmation of structures were successfully carried out with elaborate characterization by spectral data. Obtained spectral data has prompted 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.

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