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Synthesis, de-tert-butylation and antimicrobial activity of some novel 2-tert-butylamino-5-aryl-1,3,4-oxadiazole derivatives

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ABSTRACT

*A series of novel N-tert-butyl-2-aroyl hydrazine carbothioamides **(IIa-g)** and corresponding N-tert-butyl-5-aryl-1,3,4-oxadiazol-2-amines (**IIIa-g**) have been synthesized. The former compounds **(IIa-g)** were obtained by the condensation of corresponding aromatic acid hydrazide **(Ia-g)** and tert-butyl isothiocyanate. The hydrazine carbothioamides when cyclised with iodine-pot.iodide in basic medium via intramolecular cyclisation gave N-tert-butyl-5-aryl-1,3,4-oxadiazol-2-amines **(IIIa-g).** These compound **(IIIa-g)** were successfully de-tert-butylated into 5-aryl-1,3,4-oxadiazol-2-amines (**IVa-g**) and also tested for antibacterial and antifungal activities against selected microorganisms. The structures of the synthesized compounds were confirmed by elemental analyses, IR, 1H-NMR and Mass spectra.*

Keywords: Hydrazine carbothioamide, intramolecular cyclisation, de-tert-butylation.

INTRODUCTION

1,3,4-oxadiazole derivatives are known to have a broad spectrum of biological activities [1-8]. Acid hydrazides have been in general use as the starting materials in some 1,3,4-oxadiazole synthesis[9-12]. 2-Amino-5-substituted-1,3,4-oxadiazoles are of considerable pharmaceutical and material interest, which is documented by steadily increasing numbers of publications and patents. There are different methods to generate 2-amino substituted 1,3,4-oxadiazoles by oxidative cyclisation of hydrazine carbothioamides[13-24]. In view of these finding, I now report the some novel 2, 5-disubstituted 1, 3, 4-oxadiazole derivatives derived by using acid hydrazides, tert-butyl isothiocyanates[25] and Iodine-potassium iodide in basic medium. These synthesized compounds were also tested for antibacterial and antifungal activities against some selected microorganisms.

MATERIALS AND METHODS

All the chemicals required for the synthesis and other experimental work were purchased from Sigma Aldrich and S D Fine chemical company. Melting points of all synthesized compounds were determined in open capillaries by Thiel's apparatus and are uncorrected. The purity of the compounds was routinely checked in each step by TLC using Silica Gel 60G and Iodine was used to develop the TLC plates. Spectroscopic data were recorded by the following instruments; IR spectra were recorded on Perkin Elmer FT-IR spectrophotometer (υmax in cm-1). ^{1}HNMR spectra were recorded on Brucker Advance II 400 NMR spectrometer, CDRI, Chandigarh in the solvents $CDCl_3$& DMF. Chemical shifts are reported in parts per million (δ) and signals are described as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). The Mass spectra were obtained on TOF MS ES+ Mass spectrometer.

General procedure
The reagent tert-butyl isothiocyanate and acid hydrazides were prepared as described in literature. The parent compound hydrazine carbothioamide (II) was obtained by the reaction of acid hydrazide with tert-butyl isothiocyanate in absolute ethanol at reflux. Detail of typical preparation is as follows.

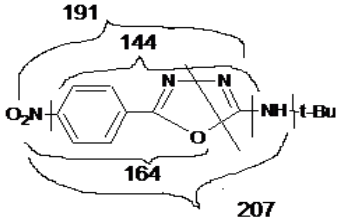
Synthesis of N-tert-butyl-2-(4-nitro benzoyl) hydrazine carbothioamide (IIa)
A mixture of 4-nitro benzohydrazide (Ia) (0.01mol) and tert-butyl isothiocyanate (0.01mol) in abs. ethanol (50 ml) was refluxed on a water bath for 2 hrs. The solvent was concentrated and the precipitated product was filtered, dried and recrystallized from ethanol, yield 92%, m.p 180^{0}C.

On extending the above reaction to different acid hydrazides (Ib-g), and the related products were isolated in good yield. (Table -1)

(**IIa**) : **IR spectra**[26-27]: (KBr) cm-1: 3329 (N-H, str), 2918, 2850(C-H str, t-Bu), 1680 (C=O str), 1528,1359(-NO_2 str) 1346 (C-N str), 1259 (C=S str); **1H-NMR** (DMSOd6) ppm: 1.4 (9H, s, t-Bu-H), 4.4 (1H, s, N-H), 8.02-8.04 (2H, d, Ar-H), 8.09-8.11 (2H, d, Ar-H), 8.1-8.2 (2H, d, N-H).

Synthesis of N-tert-butyl-5-(4-nitrophenyl)-1,3,4-oxadiazol-2-amine (IIIa).
Iodine in a 1% solution of potassium iodide in ethanol was added drop wise to a cooled (5-7°C) mixture of hydrazine carbothioamide (**IIa)** (0.01mol), ethanol (0.5 ml) and 6N sodium hydroxide solution (0.5 ml) under stirring till the color of iodine persisted. The reaction mixture was kept overnight at room temperature. The solid separated was washed with water, dried and crystallized from ethanol to yield 88% of (**IIIa)**, m.p 152-153 °C.
The other substituted compounds (IIIb-g) were prepared by extending the above reaction to different hydrazide carbothioamides (IIb-g) and the related products were isolated in good yield. (Table -1)

(**IIIa**) : **IR spectra**: (KBr) cm-1: 3329 (N-H, str), 1602 (C=N str), 1528,1345(-NO_2 str) 1250 (C-O-C str); **1H-NMR** (DMSOd6) ppm: 1.4 (9H, s, t-Bu-H), 7.09 (1H, s, N-H), 8.06-8.09 (2H, d, Ar-H), 8.1-8.2 (2H, d, Ar-H))**;Mass (m/z)**: 263[M^++1], 264, 207, 191, 164, & 144.



263 (M^+ + 1)

Synthesis of 5-(4-nitrophenyl)-1,3,4-oxadiazol-2-amine (IVa).
The N-tert-butyl-5-(4-nitrophenyl)-1,3,4-oxadiazol-2-amine (IIIa) (0.01 mol) was hydrolysed by boiling with 30% sulphuric acid (10 ml) under reflux for 3 hr. After completion of reaction, the reaction mixture was cooled and poured in ice crushed water. The product that separated was collected, dried and crystallized to give (IVa) of 49% yield, m.p 215-217 ^{0}C .

The other compounds (IVb-g) were prepared by extending the above reaction to other (IIIb-g) and the related products were isolated in good yield. (Table-1)

(**IVa**) : **1H-NMR** (DMSOd6) ppm: 8.0-8.09 (2H, d, Ar-H), 8.1-8.2 (2H, d, Ar-H)), 10.9 (2H, s, N-H).

Antimicrobial screening:
All the newly synthesized compounds (**IIIa-g**) were tested for antibacterial against gram positive and gram negative bacterial strains such as *S. aureus* and *Escherichia coli* at concentration 20 mg/mL by agar diffusion method [29-30] by using DMSO as solvent control and nutrient agar was employed as culture media. Gentamycin was used as a standard drug for comparison. After 24 hours of incubation at 37 ^{0}C, the zone of inhibition was measured in mm. All

these compounds were also screened for their antifungal activity against *Aspergillus niger* using Amphotericin as a standard. The results of antibacterial to antifungal screening studies are reported in Table-2

RESULTS AND DISCUSSION

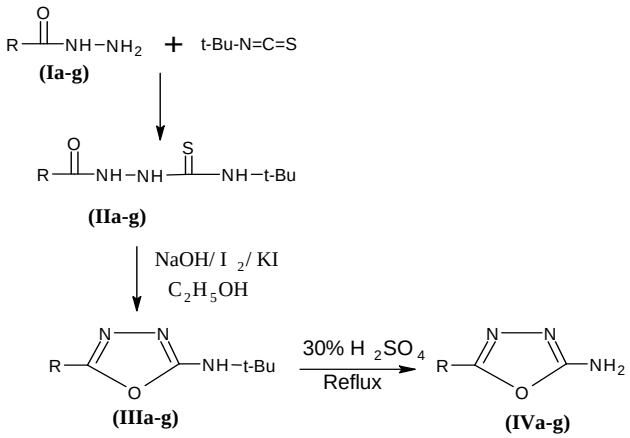
All the compounds were synthesized by following synthetic procedure enumerated in **scheme 1.** It was observed that different substituted aromatic acid hydrazides (a-g), on condensation with tert-butyl isothiocyanate in abs. ethanol yield N-tert-butyl-2-aroyl hydrazine carbothioamides (IIa-g).

Then Iodine in a 1% solution of potassium iodide in ethanol was added drop wise to a cooled (5-7 °C) mixture of hydrazine carbothioamides (**IIa-g)**, ethanol and 6N sodium hydroxide solution under stirring till the color of iodine persisted. The reaction mixture was kept overnight at room temperature to yield N-tert-butyl-5-aryl-1,3,4-oxadiazol-2-amines (**IIIa-g)**.

The compounds (IIIa-g) were hydrolyzed by boiling with 30% sulphuric acid under reflux and yielded 5-aryl-1,3,4-oxadiazol-2-amine (IVa-g).

The structures of all the synthesized compounds have been elucidated on the basis of their IR, NMR and Mass spectral data. The physicochemical data of all the synthesized derivatives were summarized in **Table 1**.

Antimicrobial screening result showed that the compounds (IIIc),(IIId) & (IIIg) exhibited low bactericidal nature against *E. Coli* and *S. aureus* while other compounds were totally inactive. Compound (IIIe) and (IIIf) were found to be weakly fungicidal against the organism *A. niger* while the other compounds were not active. (Table-.2).



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

a = p-NO $_2$C$_6$H$_4$-, b = -CH $_2$C$_6$H$_5$, c = -C $_6$H$_5$,

d = O-OHC $_6$H$_4$-, e = O-ClC $_6$H$_4$-, f = p-ClC $_6$H$_4$-, g = -C $_5$H$_4$

Scheme :1

Table 1: Physicochemical Properties Data

Compound	Molecular Formula	% Yield	M.P ^{0}C
IIa	$C_{12}H_{16}N_4O_3S$	92	180
IIb	$C_{13}H_{19}N_3OS$	78	109
IIc	$C_{12}H_{17}N_3OS$	85	140
IId	$C_{12}H_{17}N_3O_2S$	88	159
IIe	$C_{12}H_{16}ClN_3OS$	76	130
IIf	$C_{12}H_{16}ClN_3OS$	83	152
IIg	$C_{11}H_{16}N_4OS$	80	163
IIIa	$C_{12}H_{14}N_4O_3$	88	151-153
IIIb	$C_{13}H_{17}N_3O_3$	79	102-104
IIIc	$C_{12}H_{15}N_3O$	85	110-118
IIId	$C_{12}H_{15}N_3O_2$	78	141-143
IIIe	$C_{12}H_{14}ClN_3O$	70	108-110
IIIf	$C_{12}H_{14}ClN_3O$	74	154-156
IIIg	$C_{11}H_{14}N_4O$	81	159-161
IVa	$C_8H_6N_4O_3$	49	215-217
IVb	$C_9H_9N_3O$	43	136-138
IVc	$C_8H_7N_3O$	40	164-167
IVd	$C_8H_7N_3O_2$	45	169-171
IVe	$C_8H_6ClN_3O$	36	132-134
IVf	$C_8H_6ClN_3O$	39	190-192
IVg	$C_7H_6N_4O$	42	289-290

Table -2: Antimicrobial activity of 2-tert-butylamino-5-aryl-1,3,4-oxadiazole(IIIa-g)

Organism	Conc.	IIIa	IIIb	IIIc	IIId	IIIe	IIIf	IIIg
E. Coli	1.0 mg	0	0	6	7	4	4	5
	2.0 mg	3	5	12	13	7	6	8
	MIC mg	2	2	0.5	0.5	1	1	0.5
S.aureus	1.0 mg	2	2	7	10	0	0	0
	2.0 mg	7	6	12	13	2	2	0
	MIC mg	1	1	0.5	0.5	2	2	NF
A. niger	1.0 mg	5	0	0	3	9	7	0
	2.0 mg	9	6	3	6	13	12	2
	MIC mg	1	1	2	1	0.5	0.5	2

Note: NF- MIC not found among the concentrations screened

CONCLUSION

In conclusion, in present I prepared some new oxadiazole derivatives says N-tert-butyl-5-aryl-1,3,4-oxadiazol-2-amine (IIIa-f). All the synthesized compounds were successfully de-tert-butylated to 5-aryl-1,3,4-oxadiazol-2-amine (IVa-f). The structures of all the synthesized compounds were confirmed on the basis of IR, 1H NMR, and mass spectral data. Compounds were found to have moderate antimicrobial activity. However, the activities of tested compounds are much less than those of standard antibacterial and antifungal agents used.

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