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Research Article

POTENTIAL USE OF HYDRAZINE CARBOTHIOAMIDE IN THE SYNTHESIS OF HETROCYCLIC MOIETIES

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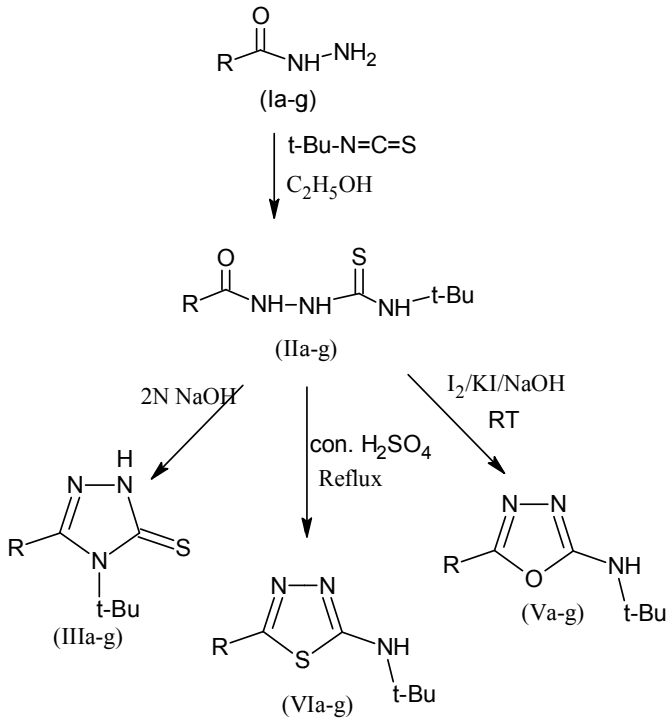
The condensation of different substituted acid hydrazides (a-g) with t-butyl isothiocyanate gave N-tert-butyl-2-aroyl hydrazine carbothioamides (IIa-g). The intramolecular cyclization of substituted hydrazine carbothioamide (Ia-g) under different condition furnished 1,2,4-triazole, 1,3,4-thiadiazole and 1,3,4-oxadiazole. The structures of all the synthesized compounds were established on the basis of IR, H^1- NMR, Mass and elemental analysis.

INTRODUCTION

The studies of five member heterocyclic compounds are of great interest because of their important physiological properties[1-2]. The hydrazine carbothioamide[3-17] has been an important key intermediates in the synthesis of various five membered ring system such as 1,2,4-triazole, 1,3,4-thiadiazole and 1,3,4-oxadiazole. In view of synthetic utility of hydrazine carbothioamide, herein I report the synthesis of different substituted hydrazine carbothioamide(Ia-g) and it's application in the synthesis of different five membered heterocyclic compounds namely 1,2,4-triazole, 1,3,4-thiadiazole and 1,3,4-oxadiazole. The synthetic rout for the desired heterocyclic compounds is outlined in scheme 1. The chemical structures have been assigned by IR, H^1- NMR spectral data and elemental analysis.

MATERIAL AND METHOD

Melting points were determined in open capillaries in a liquid paraffin bath and are uncorrected. The purity of compounds was checked by TLC. IR spectra were recorded 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).



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

Scheme 1

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General procedure

The reagent acid hydrazides[18-19] and tert-butyl isothiocyanate[20] 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)[3-5]

A mixture of 4-nitro benzohydrazide (IIa) (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 (IIb-g), and the related products were isolated in good yield. (Table -1)

(**IIa**):**IR spectra**[21-22]: (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); **^{1}H-NMR** ($DMSOd_6$) 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 4-tert-butyl-5-(4-nitro phenyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (IIIa)[3-10]

The hydrazine carbothioamide (**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.

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	$C_{12}H_{14}N_4O_2S$	85	154
IIIb	$C_{13}H_{17}N_3S$	71	112
IIIc	$C_{12}H_{15}N_3S$	78	132
IIId	$C_{12}H_{15}N_3OS$	80	136
IIIe	$C_{12}H_{14}ClN_3S$	75	122
IIIf	$C_{12}H_{14}ClN_3S$	73	142
IIIg	$C_{11}H_{14}N_4S$	80	162
IVa	$C_{12}H_{14}N_4O_2S$	74	112
IVb	$C_{13}H_{17}N_3S$	62	116
IVc	$C_{12}H_{15}N_3O$	68	160
IVd	$C_{12}H_{15}N_3OS$	72	142
IVe	$C_{12}H_{14}ClN_3S$	69	108
IVf	$C_{12}H_{14}ClN_3S$	71	153
IVg	$C_{11}H_{14}N_4S$	78	121
Va	$C_{12}H_{14}N_4O_3$	88	153
Vb	$C_{13}H_{17}N_3O_3$	79	104
Vc	$C_{12}H_{15}N_3O$	85	118
Vd	$C_{12}H_{15}N_3O_2$	78	143
Ve	$C_{12}H_{14}ClN_3O$	70	110
Vf	$C_{12}H_{14}ClN_3O$	74	156
Vg	$C_{11}H_{14}N_4O$	81	161

The mixture was kept aside for 1h, filtered, dried and recrystallised from ethanol. The other (IIIb-g) were obtained by following similar procedure. (Table -1)

(IIIa): IR (KBr): 3329, 3277 (N-H), 2972, 2919 (t-Bu-H),1528 (C=N), 1260 (C=S), 850 (p-substituted benzene). **^{1}HNMR (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

Synthesis of N-tert-butyl-5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine (IVa)[3-5].

Compound hydrazine carbothioamide **IIa** (0.01 mole) was added portion wise in 5.0 mL conc. H_2SO_4 and stirred with cooling for 2h. The mixture was poured over crushed ice and the precipitated solid was filtered, washed with water, dried and re-crystallised from ethanol. Other compounds (IVb-g) were prepared similarly. (Table -1)

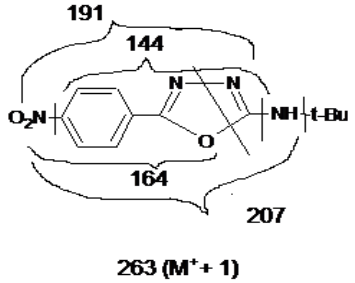
(IVa): IR (KBr): 3412 (N-H), 1610 (C=N), 2928 (C-H). **(IVa): ^{1}HNMR (CDCl3):** 1.3 (9H, s, t-Bu-H), 6.9 (1H, s, N-H), 8.01-8.04 (2H, d, Ar-H), 8.1-8.2 (2H, d, Ar-H)

Synthesis of N-tert-butyl-5-(4-nitrophenyl)-1,3,4-oxadiazol-2-amine (Va)[13-24].

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 (**Va)**, m.p 152-153 °C.

The other compounds (Vb-g) were prepared similarly and the related products were isolated in good yield. (Table -1)

(**Va**) : **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)

RESULTS AND DISCUSSION

All the compounds were synthesized by following synthetic procedure enumerated in **scheme 1.** Acid on esterification followed by treatment with hydrazine hydrate in ethanol gave acid hydrazides (Ia-g).The key intermediate hydrazine carbothioamide (IIa-g) was synthesized by the condensation of acid hydrazides (IIa-g) with t-butyl isothiocyanate in abs. ethanol.

The base and acid catalyzed dehydrative cyclization of various hydrazine carbothioamides (IIa-g) furnished corresponding 4,5-disubstituted 1,2,4-triazole-3-thione (IIIa-g) and substituted 1,3,4-thiadiazole (IVa-g) respectively.

The oxidative cyclization of hydrazine carbothioamides (IIa-g) when treated with iodine-pot.iodide in basic medium gave N-tertbutyl- 5-aryl-1,3,4-oxadiazol-2-amines (Va-g). In table 1 the molecular formula of the products, % yields and the observed melting points are listed.

IR spectra of the compounds (IIa-g) showed a characteristic absorption at 1259 cm^{-1} attributable to the C=S group. The carbonyl absorption in these compounds was observed at1680 cm^{-1}. The substituted 1,2,4-triazole (IIIa-g) and substituted 1,3,4-thiadiazole (IVa-g) were obtained by dehydrative cyclization in sodium hydroxide and concentrated sulfuric acid respectively. The absence of signals in the region 1655-1682 cm^{-1} established the lack of a C=O group in the IR spectra of compounds (III-IVa-g). The hydrazine carbothioamides (IIa-g) when treated with iodine-pot.iodide in basic medium gave N-tert-butyl- 5-aryl-1,3,4-oxadiazol-2-amines (Va-g) by oxidative cyclization. In each of the synthesized derivatives **(Va-g)** the absence of signals in the region 1240-1275 cm^{-1} in IR spectral data established the absence of C=S. ^{1}H-NMR, mass spectral data and elemental analysis of the compounds supported this.

In the ^{1}H-NMR data of compounds (III-IV-Va-g), a singlet due to proton of t-butyl group was observed in the region 1.2-1.4 ppm. For compounds (IIIa-g), a singlet for N-H proton was observed beyond aromatic region i.e 8.0-9.3 ppm. While for compounds (IV-Va-g) N-H proton appeared at 4.0-6.8 ppm.

CONCLUSION

A total 21 compounds (07 1,2,4-triazole, 07 1,3,4-thiadiazole and 07 1,3,4-oxadiazole) were successfully synthesized by the intramolecular cyclization of hydrazine carbothioamide. The structures of all the synthesized compounds were established on the basis of chemical properties and IR, NMR and mass spectral data. These compounds are expected to show antimicrobial properties.

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