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HETEROANNULATION OF SUBSTITUTED THIOCARBOHYDRAZIDE

Mustaqeem Mohammed A*& Juliet Miranda

Organic Research Laboratory, Department of Chemistry,
Royal College, Mira road (East), Thane-400 107, Maharashtra, India.
E-mail: mustaqeem19@gmail.com
jpd_@redifmail.com

Abstract: 4-Hydrazinocarbonyl-3-phenylbutanamide on reaction with aryl isothiocyanate gave substituted phenylthiosemicarbazino derivatives, which on treatment with NaOH and Conc.H_2SO_4 afforded 3-phenyl-4-{5-thioxo-4-(substituted phenyl)-4,5-dihydro-1H-[1,2,4]-triazol-3-yl}butanamide and 3-phenyl-4-{5-(substituted phenyl) [1,3,4]thiadiazol-2-yl}butanamide ,respectively. Structures have been elucidated on the basis of spectral and chemical analysis.

Keywords: Acyl chloride, Aryl isothiocyanate, Hydrazine.

Introduction:

1, 3, 4-Thiadiazoles have wide applications in many fields[I-II]. The earliest uses were in the pharmaceutical area as an antibacterial with known sulphonamides drugs[III-IV]. Thiadiazole nucleus, which incorporates a toxophoric N-C-S linkage, exhibits a large number of pharmacological activities [V-VII]. In addition 1,2,4-triazole derivatives are of interest due to their bioactivity[VIII], including antibacterials[IX] and anti fungal[X] properties.

Experimental

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR spectra were recorded on Varian 300 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer.

Method:

4-Hydrazino-3-phenylbutan-1-amide(3):

A mixture of compound **(1)** (0.01 mol) and $SOCl_2$(0.01 mol) in MDC (5ml) was stirred at room temperature for 3hrs. After completion of reaction hydrazine hydrate (0.012 mol) in methanol (8ml) was added and reflux for 6 hrs. The progress of reaction was monitor by TLC. Upon completion, the reaction mass was cooled 0 to 5 ºC. Yellow color solid thus, was filtered and washed with cold methanol to yield **(3)**.

3-Phenyl-4-[(substituted phenyl)thiosemicarbazinocarbonyl]butan-1-amide(4a-d)

Substituted isothiocyanate(0.01mol), **3** (0.01mol) and ethanol(15ml) were refluxed on water bath for 6 hrs. The reaction was monitored by TLC and after completion of the reaction; the content was poured onto crushed ice. The solid obtained was filtered, washed with water, and recrystallized from ethanol to yield **(4a-d).**

3-phenyl-4-{5-(substituted phenyl) [1,3,4]thiadiazol-2-yl}butanamide(5a-d)

A mixture of respective **4** (0.005 mol) and Conc. H_2SO_4 (5ml) were stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of reaction, the content were poured onto crushed ice and acidified. The solid obtained was filtered and washed with water to yield **5(a-d)**.

The physical data of newly synthesized compounds are given in **Table-1**.

3-phenyl-4-{5-thioxo-4-(substituted phenyl)-4,5-dihydro-1H-[1,2,4]-triazol-3-yl}butanamide (6a-d)

A mixture of respective **4** (0.005 mol) and 2M NaOH (10ml) was heated under mild reflux condition. The progress of the reaction was monitored by TLC. After completion of reaction, the content were poured onto crushed ice and acidified with acetic acid. The product obtained were separated by filtration and recrystallized from water to yield **6(a-d)**.

The physical data of newly synthesized compounds are given in **Table-1**.

Table (1): Physical data of compound 5(a-d) and 6(a-d)

Compound	R	Molecular Formula*	% Yield	Melting point (°C)
5a	H	$C_{18}H_{18}ON_4S$	75	155-57
5b	4-OCH_3	$C_{19}H_{20}O_2N_4S$	73	176-77
5c	4- CH_3	$C_{19}H_{20}ON_4S$	78	180-82
5d	4- Cl	$C_{18}H_{17}ON_4SCl$	76	134-35
6a	H	$C_{18}H_{18}ON_4S$	68	195-97
6b	4-OCH_3	$C_{19}H_{20}O_2N_4S$	74	167-69
6c	4- CH_3	$C_{19}H_{20}ON_4S$	79	170-72
6d	4- Cl	$C_{18}H_{17}ON_4SCl$	80	181-82

*Satisfactory C, H and N analysis were obtained for all the compounds.

Spectral Interpretation:

3-phenyl-4-{5-(phenyl) [1,3,4]thiadiazol-2-yl}butanamide 5a:

IR (cm^{-1}): *ν* (N-H) 3230; *ν* (CH) 2984; *ν* (C=O) 1680; *ν* (N-N=C) 1238.

1H NMR ð((ppm): 2.43 (d, 2H, CH_2); 2.83 (d, 2H, CH_2), 3.37 (m, 1H, CH), 4.25 (s, 1H, NH), 6.20 (s, 2H, NH_2), 6.08- 7.2 (m, 10H, Ar-H);

13 C NMR ð ppm: 35.21 (CH_2); 35.01 (CH); 42.29 (CH_2); 115.0-150.23 (ArC & =C); 156-158 (-C=N); 176.4 (C=O); MS: 338.3 (M+) Anal. Calcd for $C_{18}H_{18}ON_4S$:C,63.91;H,5.32; N,16.56% . Found C,63.71; H,5.29; N,16.65 % ;

3-phenyl-4-{5-(4-methoxyphenyl) [1,3,4]thiadiazol-2-yl}butanamide 5b:

IR (cm^{-1}): *v* (N-H) 3230; *v* (CH) 2984; *v* (C=O) 1685; *v* (N-N=C) 1238; *v* (C-O) 1185.

1H NMR ð(ppm): 2.42 (d, 2H, CH_2); 2.83 (d, 2H, CH_2), 3.39 (m, 1H, CH), 3.75 (s, 3H, CH_3), 4.12 (s, 1H, NH), 6.05 (s, 2H, NH_2), 6.3- 7.2 (m, 9H, Ar-H);

13 C NMR ð ppm: 34.23 (CH_2); 36.01 (CH); 42.39 (CH_2); 55.29 (CH3); 116.0-148.23 (ArC & =C); 157-158 (-C=N); 177.4 (C=O) MS: 368.2 (M+) Anal. Calcd for $C_{19}H_{20}O_2N_4S$:C, 61.19;H,5.43; N,15.21% . Found C,61.81; H,5.59; N,15.66 % ;

3-phenyl-4-{5-thioxo-4-(phenyl)-4,5-dihydro-1H-[1,2,4]-triazol-3-yl}butanamide 6a:

IR (cm^{-1}): *v* (N-H) 3240; *v* (CH) 2984; *v* (C=O) 1685; *v* (N-N=C) 1238.

1H NMR ð (ppm): 2.63 (d, 2H, CH_2); 2.89 (d, 2H, CH_2), 3.35 (m, 1H, CH), 5.29 (s, 1H, NH), 6.55 (s, 2H, NH_2), 6.80- 7.2 (m, 10H, Ar-H);

13 C NMR ð ppm: 35.23 (CH_2); 37.05 (CH); 43.49 (CH_2); 55.29 (CH3); 116.0-148.23 (ArC & =C); 157-158 (-C=N); 180.4 (C=S) MS: 338.3 (M+). Anal. Calcd for $C_{18}H_{18}ON_4S$:C,63.91;H,5.32; N,16.56% . Found C,63.71; H,5.29; N,16.65 % ;

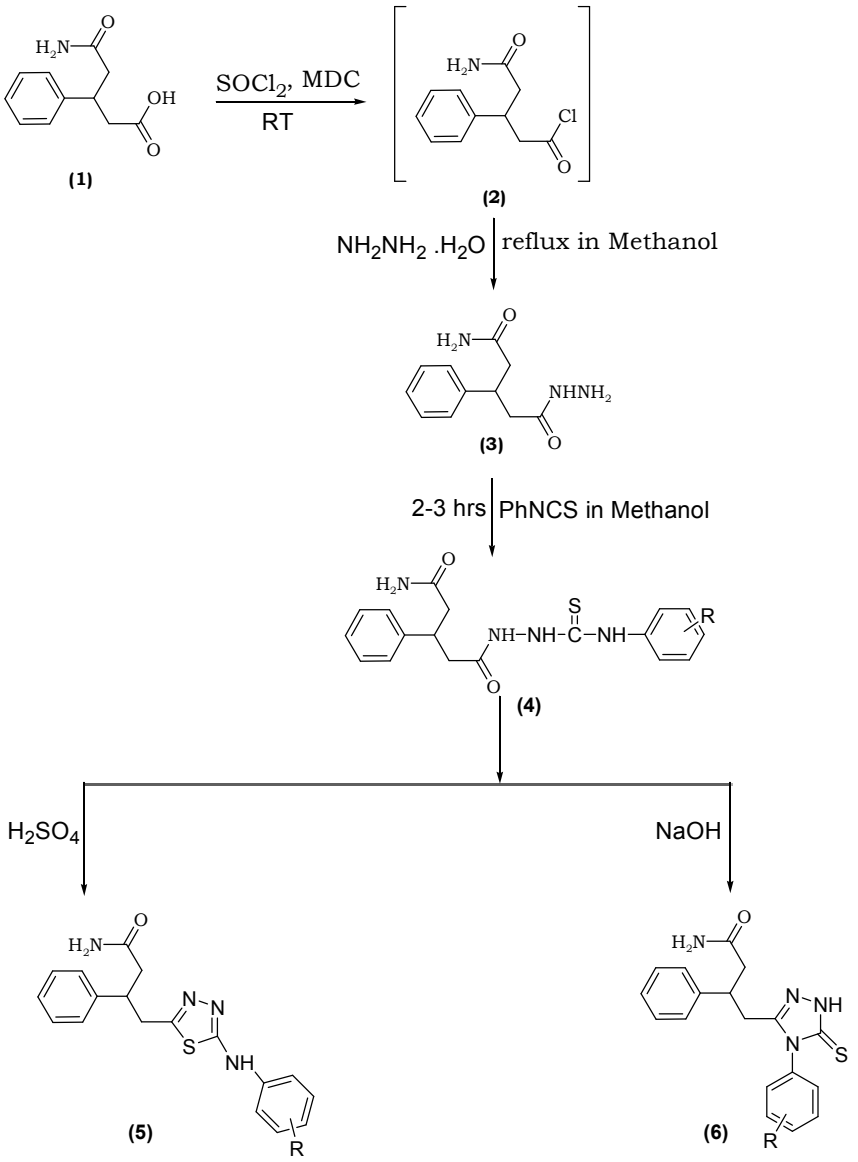
3-phenyl-4-{5-thioxo-4-(4-methylphenyl)-4,5-dihydro-1H-[1,2,4]-triazol-3-yl}butanamide 6c:

IR (cm^{-1}): *v* (N-H) 3240; *v* (CH) 2984; *v* (C=O) 1685; *v* (N-N=C) 1238; *v* (C-O) 1175.

1H NMR ð (ppm): 2.23 (d, 2H, CH_3); 2.53 (d, 2H, CH_2); 2.83 (d, 2H, CH_2), 3.27 (m, 1H, CH), 5.25 (s, 1H, NH), 6.60 (s, 2H, NH_2), 6.80- 7.2 (m, 9H, Ar-H);

13 C NMR ð ppm: 33.24 (CH_2); 36.12 (CH); 42.59 (CH_2); 22.39 (CH_3); 115.0-149.43 (ArC & =C); 155-158 (-C=N); 177.4 (C=O); 180.4 (C=S) MS: 352.3 (M+). Anal. Calcd for $C_{19}H_{20}ON_4S$ C,64.77;H,5.68; N,15.91% . Found C,64.71; H,5.59; N, 15.69 % ;

Reaction Scheme



Conclusion

The synthesized compounds **5a-d** and **6a-d** can show convincing activity against Gram positive, Gram negative organisms due to presence of triazole and thiazole moiety. The data reported in this article may be helpful guide for the medical chemists who are working in this area.

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