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Research Article

CLASSICAL AND MICROWAVE ASSISTED SYNTHESIS OF NOVEL SCHIFF'S BASE AND THEIR CHARACTERIZATION

SINGARAVEL MOHAN[a,b] *, SARKKARAI ANANTHAN[b]

[a] Research & Development Centre, Orchid Chemicals & Pharmaceuticals Ltd, Sholinganallur, Chennai-600 119, Tamil Nadu, India, [b]Department of Chemistry, Presidency College, Chennai-600 005, India. Email: singaravelmohan@yahoo.co.in

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ABSTRACT

Reaction of mercaptoheterocyclic compounds with ethyl bromoacetate in the presence of base afforded thioacetate derivative of mercaptoheterocyclic compounds. These on subsequent treatment with hydrazine hydrate yielded acylated hydrazine derivative of mercaptoheterocyclic compounds. Reaction of these acylated hydrazine derivatives of mercaptoheterocyclic compounds with various aromatic aldehydes afforded respective Schiff's base derivatives.

Keywords: Schiff's base, Thioacetate, Acylated hydrazine, Mercaptoheterocycles

INTRODUCTION

Tumour necrosis factor α (TNF-α) is a key cytokine that contributes to immune and inflammatory reactions and is important for both innate and adaptive immunity.[1] Currently, a significant effort is focused on the development of anti-TNF-α agents as therapeutics for treatment of chronic inflammatory conditions, such as rheumatoid arthritis and inflammatory bowel disease.[2] Recently, several small molecule N-formyl peptide receptor agonists that potently induced tumor necrosis factor α (TNF-α) production in murine and human macrophages are identified. Interestingly, all of these compounds contain an aryl carboxylic acid hydrazide core structure, which is distinct from other known inducers of TNF-α production. Computational structure–activity analysis of a series of aryl carboxylic acid hydrazide derivatives reports their ability to induce macrophage tumor necrosis factor α production and found that a number of compounds induced production of modest to high levels of TNF-α in murine and human macrophages.[3] The computational structure-activity analysis reports has been extended to several compounds including aryl carboxylic acid hydrazide derivative of nicotinic acid and isonicotinic acid and it reveals that aryl carboxylic acid hydrazide derivatives of nicotinic acid and isonicotinic acid are the most active.[4] Similarly Schiff's bases have been reported to possess antimicrobial[5-7] apart from other biological activities. Hydrazine functionalities are also important intermediates for the synthesis of some bioactive compounds such as β-lactams.[8-11] Furthermore, they have been reported to show a variety of interesting biological activities. The synthetic versatility of hydrazine has led to the extensive use of it in organic synthesis. In our recent communication we reported some of the novel sulphur bridged pyrazole derivatives prepared from acylated hydrazine derivatives[12] and a new approach for the preparation of pyrazole derivatives[13].

MATERIALS AND METHODS

General

Melting points were determined on a Buchi Melting point B-540 instrument and are uncorrected. The purity of the compounds was analyzed by thin layer chromatography (pre-coated silica gel, Merck, chloroform/methanol, 8:2). The mass spectra were recorded in PE-SCIEX API-3000 LC/MS/MS with Turbo ion spray. The ^1H and ^{13}C NMR spectra were recorded in DMSO-d6 on a Bruker Avance 400 MHz Spectrometer with multinuclear BBO Probe and TMS as an internal standard and the values are in δ ppm.

2-[(1-Methyl-1H-tetrazol-5-yl)thio]-N'-[(1E)-phenylmethylene]acetohydrazide (4a):

To a mixture of 2-[(1-methyl-1H-tetrazol-5-yl)thio]acetohydrazide (2 g; 10.6 mmol) and benzaldehyde (1.13 g; 10.6 mmol) in ethanol (20 mL) a few drops of acetic acid was added. The reaction mixture was heated under reflux till completion of reaction. The reaction was monitored by thin layer chromatography using chloroform/methanol (8:2). The reaction mass was cooled to room temperature. The crystallized product, 2-[(1-methyl-1H-tetrazol-5-yl)thio]-N'-[(1E)-phenylmethylene]acetohydrazide was filtered and washed with ethanol. (Yield 2.7 g, 91.95 %). *m/z* 277.3 $(M+H)^+$; mp 170.5 °C; ^1H NMR 3.98 (3H, s, NCH_3), 4.18 and 4.62 (2H, s, SCH_2), 7.44-7.70 (5H, m, Ar), 8.04 and 8.19 (1H, s, =CH), 11.76 (1H, s, NH); Anal. Calcd. for $C_{11}H_{12}N_6OS$: C, 47.81; H, 4.38; N, 30.41. Found: C, 47.65; H, 4.29; N, 30.74

2-[(1-Methyl-1H-tetrazol-5-yl)thio]-N'-[(1E)-(4-fluorophenyl)methylene]acetohydrazide (4b):

By following the procedure disclosed for **4a,** use of 4-fluorobenzaldehyde instead of benzaldehyde afforded 2-[(1-methyl-1H-tetrazol-5-yl)thio]-N'-[(1E)-(4-fluorophenyl)methylene]acetohydrazide (Yield 2.5 g, 80.21 %). *m/z* 295.4 $(M+H)^+$; mp 185.2 °C; ^1H NMR 3.99 (3H, s, NCH_3), 4.19 and 4.62 (2H, s, SCH_2), 7.27-7.78 (4H, m, Ar), 8.03 and 8.19 (1H, s, =CH), 11.77 (1H, s, NH)

2-[(1-Methyl-1H-tetrazol-5-yl)thio]-N'-[(1E)-(2-chlorophenyl)methylene]acetohydrazide (4c):

By following the procedure disclosed for **4a,** use of 2-chlorobenzaldehyde instead of benzaldehyde afforded 2-[(1-methyl-1H-tetrazol-5-yl)thio]-N'-[(1E)-(2-chlorophenyl)methylene]acetohydrazide (Yield 2.6 g, 78.73 %). *m/z* 311.3 $(M+H)^+$; mp 167.5 °C; ^1H NMR 3.99 (3H, s, NCH_3), 4.19 and 4.63 (2H, s, SCH_2), 7.42-7.99 (4H, m, Ar), 8.42 and 8.58 (1H, s, =CH), 11.94 (1H, s, NH)

2-[(1-Methyl-1H-tetrazol-5-yl)thio]-N'-[(1E)-(3-nitrophenyl)methylene]acetohydrazide (4d):

By following the procedure disclosed for **4a,** use of 3-nitrobenzaldehyde instead of benzaldehyde afforded 2-[(1-methyl-1H-tetrazol-5-yl)thio]-N'-[(1E)-(3-nitrophenyl)methylene]acetohydrazide (Yield 2.1 g, 61.50 %). *m/z* 322.1 $(M+H)^+$; mp 193.2 °C; ^1H NMR 3.99 (3H, s, NCH_3), 4.22 and 4.66 (2H, s, SCH_2), 7.73-8.51 (4H, m, Ar), 8.54 and 8.70 (1H, s, =CH), 11.98 (1H, s, NH)

2-[(1-Methyl-1H-tetrazol-5-yl)thio]-N'-[(1E)-(4-nitrophenyl)methylene]acetohydrazide (4e):

By following the procedure disclosed for **4a,** use of 4-nitrobenzaldehyde instead of benzaldehyde afforded 2-[(1-methyl-1H-tetrazol-5-yl)thio]-N'-[(1E)-(4-nitrophenyl)methylene]acetohydrazide (Yield 2.0 g, 58.58 %). *m/z* 320.0 $(M-H)^-$; mp 216.3 °C; ^1H NMR 3.99 (3H, s, NCH_3), 4.23 and 4.66

(2H, s, SCH_2), 7.96-8.28 (4H, m, Ar), 8.30 and 8.34 (1H, s, =CH), 12.04 (1H, s, NH)

2-[(1-Methyl-1H-tetrazol-5-yl)thio]-N'-[(1E)-(4-hydroxyphenyl)methylene]acetohydrazide (4f):

By following the procedure disclosed for **4a,** use of 4-hydroxybenzaldehyde instead of benzaldehyde afforded 2-[(1-methyl-1H-tetrazol-5-yl)thio]-N'-[(1E)-(4-hydroxyphenyl)-methylene]acetohydrazide (Yield 2.3 g, 74.04 %). *m/z* 293.0 $(M+H)^+$; mp 245.3 °C (dec); ^1H NMR 3.98 (3H, s, NCH_3), 4.15 and 4.57 (2H, s, SCH_2), 6.81-7.53 (4H, m, Ar), 7.92 and 8.07 (1H, s, =CH), 9.92 and 9.94 (1H, s, -OH), 11.54 and 44.57 (1H, s, NH)

2-[(1-Methyl-1H-tetrazol-5-yl)thio]-N'-[(1E)-(4-methoxyphenyl)methylene]acetohydrazide (4g):

By following the procedure disclosed for **4a,** use of 4-methoxybenzaldehyde instead of benzaldehyde afforded 2-[(1-methyl-1H-tetrazol-5-yl)thio]-N'-[(1E)-(4-methoxyphenyl)-methylene]acetohydrazide (Yield 2.4 g, 73.73 %) *m/z* 307.2 $(M+H)^+$; mp 175.8 °C; ^1H NMR 3.80 (3H, s, OCH_3), 3.99 (3H, s, NCH_3), 4.17 and 4.59 (2H, s, SCH_2), 6.99-7.65 (4H, m, Ar), 7.97 and 8.12 (1H, s, =CH), 11.63 (1H, s, NH)

2-[(1-Methyl-1H-tetrazol-5-yl)thio]-N'-[(1E)-(4-hydroxy-3-methoxyphenyl)methylene]acetohydrazide (4h):

By following the procedure disclosed for **4a,** use of 4-hydroxy-3-methoxybenzaldehyde instead of benzaldehyde afforded 2-[(1-methyl-1H-tetrazol-5-yl)thio]-N'-[(1E)-(4-hydroxy-3-methoxyphenyl)methylene]acetohydrazide (Yield 2.5 g, 72.99 %). *m/z* 322.0 $(M+H)^+$; mp 217.3 °C; ^1H NMR 3.81 (3H, s, OCH_3), 3.99 (3H, s, NCH_3), 4.16 and 4.58 (2H, s, SCH_2), 6.82-7.27 (3H, m, Ar), 7.91 and 8.06 (1H, s, =CH), 9.55 (1H, s, -OH), 11.57 (1H, s, NH)

2-[(1-Methyl-1H-tetrazol-5-yl)thio]-N'-[(1E)-(3,4,5-trimethoxyphenyl)methylene]acetohydrazide (4i):

By following the procedure disclosed for **4a,** use of 3,4,5-trimethoxybenzaldehyde instead of benzaldehyde afforded 2-[(1-methyl-1H-tetrazol-5-yl)thio]-N'-[(1E)-(3,4,5-methoxyphenyl)methylene]acetohydrazide (Yield 2.7 g, 82.19 %). *m/z* 367.0 $(M+H)^+$; mp 180.6 °C; ^1H NMR 3.69-3.83 (9H, m, $3OCH_3$), 3.99 (3H, s, NCH_3), 4.19 and 4.59 (2H, s, SCH_2), 7.01-7.02 (2H, m, Ar), 7.94 and 8.10 (1H, s, =CH), 11.75 (1H, s, NH)

2-[(1-Methyl-1H-tetrazol-5-yl)thio]-N'-[(1E)-(4-methyl-1,3-thiazol-5-yl)methylene]acetohydrazide (4j):

By following the procedure disclosed for **4a,** use of 4-methyl-1,3-thiazole-5-carbaldehyde instead of benzaldehyde afforded 2-[(1-methyl-1H-tetrazol-5-yl)thio]-N'-[(1E)-(4-methyl-1,3-thiazol-5-yl)methylene]acetohydrazide. (Yield 2.2 g, 69.62 %). *m/z* 298.2 $(M+H)^+$; mp 158.9 °C; ^1H NMR 2.47 (3H, s, thiazole CH_3), 3.98 (3H, s, NCH_3), 4.16 and 4.51 (2H, s, SCH_2), 8.28 and 8.46 (1H, s, =CH), 9.06 (1H, s, thiazole CH), 11.71 (1H, s, NH)

2-[(5-Phenyl-1,3,4-oxadiazol-2-yl)thio]-N'-[(1E)-phenylmethylene]acetohydrazide (5a):

To a mixture of 2-[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]aceto-hydrazide (2 g; 10 mmol) and benzaldehyde (10 mmol) in ethanol (20 mL) a few drops of acetic acid was added. The reaction mixture was heated under reflux till completion of reaction. The reaction was monitored by thin layer chromatography using chloroform/methanol (8:2). The reaction mass was cooled to room temperature. The crystallized product, 2-[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]-N'-[(1E)-phenylmethylene]acetohydrazide was filtered and washed with ethanol. (Yield 2.3 g, 84.96 %). *m/z* 339.3 $(M+H)^+$; mp 173.0 °C; ^1H NMR 4.24 & 4.68 (2H, s, SCH_2), 7.43-7.98 (10H, m, Ar), 8.05 & 8.22 (1H, s, =CH), 11.81 & 11.86 (1H, s, NH); Anal. Calcd. for $C_{17}H_{14}N_4O_2S$: C, 60.34; H, 4.17; N, 16.56. Found: C, 60.11; H, 4.25; N, 16.85

2-[(5-Phenyl-1,3,4-oxadiazol-2-yl)thio]-N'-[(1E)-(4-fluorophenyl)methylene]acetohydrazide (5b):

By following the procedure disclosed for **5a,** use of 4-fluorobenzaldehyde instead of benzaldehyde afforded 2-[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]-N'-[(1E)-(4-fluorophenyl)methylene]acetohydrazide. (Yield 2.5 g, 87.69 %). *m/z* 357.1 $(M+H)^+$; mp 171.1 °C; ^1H NMR 4.24 and 4.67 (2H, s, SCH_2), 7.25-7.98 (9H, m, Ar), 8.04 and 8.22 (1H, s, =CH), 11.82 and 11.87 (1H, s, NH)

2-[(5-Phenyl-1,3,4-oxadiazol-2-yl)thio]-N'-[(1E)-(2-chlorophenyl)methylene]acetohydrazide (5c):

By following the procedure disclosed for **5a,** use of 2-chlorobenzaldehyde instead of benzaldehyde afforded 2-[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]-N'-[(1E)-(2-chlorophenyl)methylene]acetohydrazide. (Yield 2.6 g, 87.17 %). *m/z* 373.1 $(M+H)^+$; mp 186.4 °C; ^1H NMR 4.25 and 4.69 (2H, s, SCH_2), 7.39-8.02 (9H, m, Ar), 8.44 and 8.61 (1H, s, =CH), 11.98 and 12.10 (1H, s, NH)

2-[(5-Phenyl-1,3,4-oxadiazol-2-yl)thio]-N'-[(1E)-(3-nitrophenyl)methylene]acetohydrazide (5d):

By following the procedure disclosed for **5a,** use of 3-nitrobenzaldehyde instead of benzaldehyde afforded 2-[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]-N'-[(1E)-(3-nitrophenyl)methylene]acetohydrazide. (Yield 2.2 g, 71.73 %). *m/z* 384.2 $(M+H)^+$; mp 193.0 °C; ^1H NMR 4.28 and 4.72 (2H, s, SCH_2), 7.55-8.36 (9H, m, Ar), 8.52 and 8.55 (1H, s, =CH), 12.05 and 12.11 (1H, s, NH)

2-[(5-Phenyl-1,3,4-oxadiazol-2-yl)thio]-N'-[(1E)-(4-nitrophenyl)methylene]acetohydrazide (5e):

By following the procedure disclosed for **5a,** use of 4-nitrobenzaldehyde instead of benzaldehyde afforded 2-[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]-N'-[(1E)-(4-nitrophenyl)methylene]acetohydrazide. (Yield 2.1 g, 68.47 %). *m/z* 384.2 $(M+H)^+$; mp 218.3 °C; ^1H NMR 4.28 and 4.70 (2H, s, SCH_2), 7.55-8.29 (9H, m, Ar), 8.31 and 8.33 (1H, s, =CH), 12.09 (1H, s, NH)

2-[(5-Phenyl-1,3,4-oxadiazol-2-yl)thio]-N'-[(1E)-(4-hydroxyphenyl)methylene]acetohydrazide (5f):

By following the procedure disclosed for **5a,** use of 4-hydroxybenzaldehyde instead of benzaldehyde afforded 2-[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]-N'-[(1E)-(4-hydroxyphenyl)methylene]acetohydrazide. (Yield 2.5 g, 88.18 %). *m/z* 355.2 $(M+H)^+$; mp 214.7 °C; ^1H NMR 4.21 and 4.64 (2H, s, SCH_2), 6.80-7.95 (9H, m, Ar), 7.97 and 8.10 (1H, s, =CH), 9.94 and 9.96 (1H, s, -OH), 11.62 and 11.65 (1H, s, NH)

2-[(5-Phenyl-1,3,4-oxadiazol-2-yl)thio]-N'-[(1E)-(4-methoxyphenyl)methylene]acetohydrazide (5g):

By following the procedure disclosed for **5a,** use of 4-methoxybenzaldehyde instead of benzaldehyde afforded 2-[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]-N'-[(1E)-(4-methoxyphenyl)methylene]acetohydrazide. (Yield 2.6 g, 88.22 %). *m/z* 369.2 $(M+H)^+$; mp 157.8 °C; ^1H NMR 4.22 and 4.64 (2H, s, SCH_2), 6.97-7.97 (9H, m, Ar), 7.99 and 8.15 (1H, s, =CH), 11.68 and 11.73 (1H, s, NH)

2-[(5-Phenyl-1,3,4-oxadiazol-2-yl)thio]-N'-[(1E)-(4-hydroxy-3-methoxyphenyl)methylene]acetohydrazide (5h):

By following the procedure disclosed for **5a,** use of 4-hydroxy-3-methoxybenzaldehyde instead of benzaldehyde afforded 2-[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]-N'-[(1E)-(4-hydroxy-3-methoxyphenyl)methylene]acetohydrazide. (Yield 2.8 g, 91.05 %). *m/z* 385.3 $(M+H)^+$; mp 199.9 °C; ^1H NMR 3.81 (3H, s, OCH_3), 4.28 and 4.72 (2H, s, SCH_2), 6.83-8.11 (8H, m, Ar), 8.14 and 8.17 (1H, s, =CH), 9.55 and 9.59 (1H, s, -OH), 11.65 and 11.68 (1H, s, NH)

2-[(5-Phenyl-1,3,4-oxadiazol-2-yl)thio]-N'-[(1E)-(3,4,5-trimethoxyphenyl)methylene]acetohydrazide (5i):

By following the procedure disclosed for **5a,** use of 3,4,5-trimethoxybenzaldehyde instead of benzaldehyde afforded 2-[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]-N'-[(1E)-(3,4,5-trimethoxy-phenyl)methylene]acetohydrazide. (Yield 3.1 g, 90.44 %). *m/z* 429.1 $(M+H)^+$; mp 200.2 °C; ^1H NMR 3.69-3.83 (9H, m, $3OCH_3$), 4.24 and

4.68 (2H, s, SCH_2), 7.02-7.96 (7H, m, Ar), 7.99 and 8.14 (1H, s, =CH), 11.83 (1H, s, NH)

2-[(5-Phenyl-1,3,4-oxadiazol-2-yl)thio]-N'-[(1E)-(4-methyl-1,3-thiazol-5-yl)methylene]acetohydrazide (5j):

By following the procedure disclosed for **5a,** use of 4-methyl-1,3-thiazole-5-carbaldehyde instead of benzaldehyde afforded 2-[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]-N'-[(1E)-(4-methyl-1,3-thiazol-5-yl)methylene]acetohydrazide. (Yield 2.4 g, 83.47 %). *m/z* 360.3 $(M+H)^+$; mp 194.5 °C; ^{1}H NMR 2.48 (3H, s, CH_3), 4.21 and 4.57 (2H, s, SCH_2), 7.56-7.97 (5H, m, Ar), 8.29 and 8.49 (1H, s, =CH), 9.06 and 9.07 (1H, s, thiazole CH), 11.78 and 11.89 (1H, s, NH)

2-[1,3,4-Thiadiazol-2-ylthio]-N'-[(1E)-phenylmethylene]acetohydrazide (6a):

To a mixture of 2-(1,3,4-thiadiazol-2-ylthio)acetohydrazide (2 g; 10 mmol) and benzaldehyde (10 mmol) in ethanol (20 mL) a few drops of acetic acid was added. The reaction mixture was heated under reflux till completion of reaction. The reaction was monitored by thin layer chromatography using chloroform/methanol (8:2). The reaction mass was cooled to room temperature. The crystallized product, 2-[1,3,4-thiadiazol-2-ylthio]-N'-[(1E)-phenylmethylene]acetohydrazide was filtered and washed with ethanol. (Yield 2.1 g, 71.79 %). *m/z* 279.3 $(M+H)^+$; mp 136.4 °C; ^{1}H NMR 4.23 and 4.66 (2H, s, SCH_2), 7.44-7.71 (5H, m, Ar), 8.04 and 8.21 (1H, s, N=CH), 9.52 and 9.53 (1H, s, CH), 11.75 and 11.82 (1H, s, NH); Anal. Calcd. for $C_{11}H_{10}N_4OS_2$: C, 47.46; H, 3.62; N, 20.13. Found: C, 47.36; H, 3.71; N, 20.25

2-[1,3,4-Thiadiazol-2-ylthio]-N'-[(1E)-(4-fluorophenyl)methylene]acetohydrazide (6b):

By following the procedure disclosed for **6a,** use of 4-fluorobenzaldehyde instead of benzaldehyde afforded 2-[1,3,4-thiadiazol-2-ylthio]-N'-[(1E)-(4-fluorophenyl)methylene]acetohydrazide. (Yield 2.3 g, 73.85 %). *m/z* 297.2 $(M+H)^+$; mp 172.2 °C; ^{1}H NMR 4.23 and 4.66 (2H, s, SCH_2), 7.27-7.79 (4H, m, Ar), 8.04 and 8.21 (1H, s, N=CH), 9.52 and 9.53 (1H, s, CH), 11.76 and 11.83 (1H, s, NH)

2-[1,3,4-Thiadiazol-2-ylthio]-N'-[(1E)-(2-chlorophenyl)methylene]acetohydrazide (6c):

By following the procedure disclosed for **6a,** use of 2-chlorobenzaldehyde instead of benzaldehyde afforded 2-[1,3,4-thiadiazol-2-ylthio]-N'-[(1E)-(2-chlorophenyl)methylene]acetohydrazide. (Yield 2.4 g, 73.01 %). *m/z* 313.1 $(M+H)^+$; mp 157.3 °C; ^{1}H NMR 4.22 and 4.65 (2H, s, SCH_2), 7.44-7.71 (4H, m, Ar), 8.04 and 8.22 (1H, s, N=CH), 9.51 and 9.52 (1H, s, CH), 11.71 and 11.78 (1H, s, NH)

2-[1,3,4-Thiadiazol-2-ylthio]-N'-[(1E)-(3-nitrophenyl)methylene]acetohydrazide (6d):

By following the procedure disclosed for **6a,** use of 3-nitrobenzaldehyde instead of benzaldehyde afforded 2-[1,3,4-thiadiazol-2-ylthio]-N'-[(1E)-(3-nitrophenyl)methylene]acetohydrazide. (Yield 2.2 g, 64.74 %). *m/z* 324.2 $(M+H)^+$; mp 183.3 °C; ^{1}H NMR 4.22 and 4.65 (2H, s, SCH_2), 7.44-8.04 (4H, m, Ar), 8.22 (1H, s, N=CH), 9.51 and 9.52 (1H, s, CH), 11.71 and 11.78 (1H, s, NH)

2-[1,3,4-Thiadiazol-2-ylthio]-N'-[(1E)-(4-nitrophenyl)methylene]acetohydrazide (6e):

By following the procedure disclosed for **6a,** use of 4-nitrobenzaldehyde instead of benzaldehyde afforded 2-[1,3,4-thiadiazol-2-ylthio]-N'-[(1E)-(4-nitrophenyl)methylene]acetohydrazide. (Yield 2.2 g, 64.74 %). *m/z* 324.2 $(M+H)^+$; mp 172.6 °C; ^{1}H NMR 4.27 and 4.71 (2H, s, SCH_2), 7.97-8.28 (4H, m, Ar), 8.30 (1H, s, N=CH), 9.52 and 9.53 (1H, s, CH), 12.04 (1H, s, NH)

2-[1,3,4-Thiadiazol-2-ylthio]-N'-[(1E)-(4-hydroxyphenyl)methylene]acetohydrazide (6f):

By following the procedure disclosed for **6a,** use of 4-hydroxybenzaldehyde instead of benzaldehyde afforded 2-[1,3,4-thiadiazol-2-ylthio]-N'-[(1E)-(4-hydroxyphenyl)-methylene]-acetohydrazide. (Yield 2.5 g, 80.81 %). *m/z* 295.2 $(M+H)^+$; mp 209.0 °C; ^{1}H NMR 4.19 and 4.62 (2H, s, SCH_2), 6.81-7.53 (4H, m, Ar), 7.93 and 8.09 (1H, s, N=CH), 9.51 and 9.53 (1H, s, CH), 9.93 and 9.95 (1H, s, -OH), 11.55 and 11.61 (1H, s, NH)

2-[1,3,4-Thiadiazol-2-ylthio]-N'-[(1E)-(4-methoxyphenyl)methylene]acetohydrazide (6g):

By following the procedure disclosed for **6a,** use of 4-methoxybenzaldehyde instead of benzaldehyde afforded 2-[1,3,4-thiadiazol-2-ylthio]-N'-[(1E)-(4-methoxyphenyl)methylene]-acetohydrazide. (Yield 2.4 g, 74.05 %). *m/z* 309.4 $(M+H)^+$; mp 164.2 °C; ^{1}H NMR 3.80 (3H, s, OCH_3), 4.21 and 4.64 (2H, s, SCH_2), 6.99-7.66 (4H, m, Ar), 7.98 and 8.15 (1H, s, N=CH), 9.51 and 9.53 (1H, s, CH), 11.62 and 11.69 (1H, s, NH)

2-[1,3,4-Thiadiazol-2-ylthio]-N'-[(1E)-(4-hydroxy-3-methoxyphenyl)methylene]acetohydrazide (6h):

By following the procedure disclosed for **6a,** use of 4-hydroxy-3-methoxybenzaldehyde instead of benzaldehyde afforded 2-[1,3,4-thiadiazol-2-ylthio]-N'-[(1E)-(4-hydroxy-3-methoxyphenyl)methylene]acetohydrazide. (Yield 2.6 g, 76.21 %). *m/z* 325.2 $(M+H)^+$; mp 203.3 °C; ^{1}H NMR 3.81 (3H, s, OCH_3), 4.19 and 4.63 (2H, s, SCH_2), 6.82-7.29 (3H, m, Ar), 7.92 and 8.08 (1H, s, N=CH), 9.51 and 9.53 (1H, s, CH), 9.54 and 9.57 (1H, s, -OH), 11.58 and 11.63 (1H, s, NH)

2-[1,3,4-Thiadiazol-2-ylthio]-N'-[(1E)-(3,4,5-trimethoxyphenyl)methylene]acetohydrazide (6i):

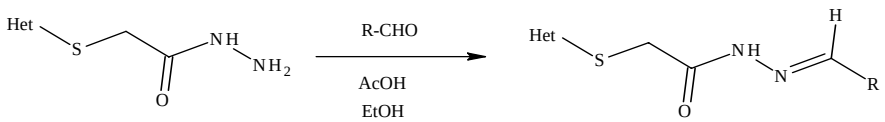
By following the procedure disclosed for **6a,** use of 3,4,5-trimethoxybenzaldehyde instead of benzaldehyde afforded 2-[1,3,4-thiadiazol-2-ylthio]-N'-[(1E)-(3,4,5-trimethoxyphenyl)methylene]-acetohydrazide. (Yield 3.0 g, 77.48 %). *m/z* 369.1 $(M+H)^+$; mp 174.9 °C; ^{1}H NMR 3.69-3.86 (9H, m, 3 OCH_3), 4.23 and 4.66 (2H, s, SCH_2), 7.02-7.26 (2H, m, Ar), 7.95 and 8.13 (1H, s, N=CH), 9.51 and 9.53 (1H, s, CH), 11.76 and 11.79 (1H, s, NH)

2-[1,3,4-Thiadiazol-2-ylthio]-N'-[(1E)-(4-methyl-1,3-thiazol-5-yl)methylene]acetohydrazide (6j):

By following the procedure disclosed for **6a,** use of 4-methyl-1,3-thiazole-5-carbaldehyde instead of benzaldehyde afforded 2-[1,3,4-thiadiazol-2-ylthio]-N'-[(1E)-(4-methyl-1,3-thiazol-5-yl)methylene]acetohydrazide. (Yield 2.4 g, 76.27 %). *m/z* 300.2 $(M+H)^+$; mp 182.4 °C; ^{1}H NMR 2.47 and 2.50 (3H, s, CH_3), 4.20 and 4.56 (2H, s, SCH_2), 8.29-8.49 (1H, s, N=CH), 9.06 (1H, s, thiazole CH), 9.51 and 9.53 (1H, s, thiadiazole CH), 11.71 and 11.85 (1H, s, NH)

RESULTS AND DISCUSSION

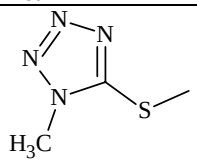
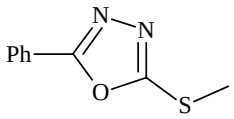
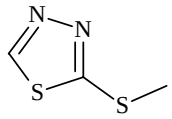
On treatment of the ethanolic suspension of acylated hydrazine derivatives of mercaptoheterocyclic compounds (**1-3**) with various aromatic aldehydes in the presence of catalytic amount of acetic acid afforded the Schiff's base of acylated hydrazine derivative of mercaptoheterocyclic compounds (**4a-j, 5a-j** and **6a-j**). After 8-10 hours, the temperature of reaction mixture was brought down to room temperature. The product crystallized out from the reaction medium. In certain cases the product formation was observed even at reflux temperature. The product was isolated by filtration and dried under vacuum to remove the residual solvent as represented in **Scheme-1**. The acylated hydrazine derivative of mercaptoheterocyclic compounds used for the synthesis of Schiff's base is prepared as per the procedure disclosed in our earlier communication[12-13].



1-3 **4a-j** **5a-j** **6a-j**

Scheme 1: Synthesis of Schiff's base of acylated hydrazine derivatives of mercaptoheterocyclic compounds

Table 1: Representation of Het and R in scheme-1

Compound No	Het	R
4a		Phenyl
4b		4-Fluorophenyl
4c		2-Chlorophenyl
4d		3-Nitrophenyl
4e		4-Nitrophenyl
4f		4-Hydroxyphenyl
4g		4-Methoxyphenyl
4h	5-mercapto-1-methyltetrazolyl	4-Hydroxy-3-methoxyphenyl
4i		3,4,5-Trimethoxyphenyl
4j		4-Methyl-1,3-thiazolyl
5a		Phenyl
5b		4-Fluorophenyl
5c		2-Chlorophenyl
5d		3-Nitrophenyl
5e		4-Nitrophenyl
5f	5-phenyl-2-mercapto-oxadiazolyl	4-Hydroxyphenyl
5g		4-Methoxyphenyl
5h		4-Hydroxy-3-methoxyphenyl
5i		3,4,5-Trimethoxyphenyl
5j		4-Methyl-1,3-thiazolyl
6a		Phenyl
6b		4-Fluorophenyl
6c		2-Chlorophenyl
6d		3-Nitrophenyl
6e		4-Nitrophenyl
6f	2-mercaptothiadiazolyl	4-Hydroxyphenyl
6g		4-Methoxyphenyl
6h		4-Hydroxy-3-methoxyphenyl
6i		3,4,5-Trimethoxyphenyl
6j		4-Methyl-1,3-thiazolyl

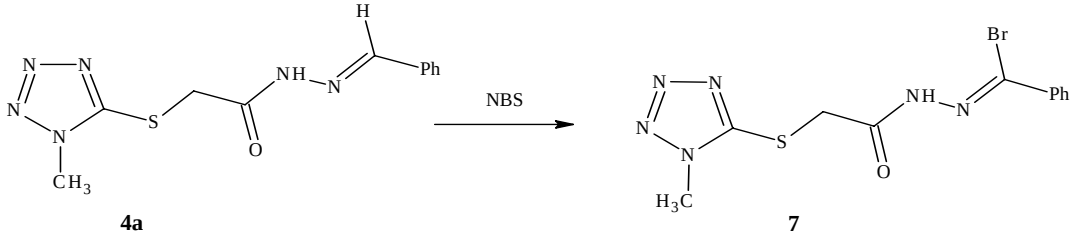
The Schiff's base formation reaction was performed under microwave irradiation using N,N-dimethylformamide as solvent at 300 W. Hence a mixture of hydrazine derivative and the corresponding aromatic aldehyde in N,N-dimethylformamide and in the presence of catalytic amount of acetic acid was exposed to microwave irradiation at 300 W for 20 seconds and then cooled. This operation was repeated for 3-5 minutes to complete the Schiff's base formation. After completion of the reaction, the reaction mass was added slowly into ice cold water. The precipitated Schiff's base was filtered and washed with chilled water. It was recrystallized from methanol.

The classical reaction using ethanol under reflux condition took 8-12 hours for the completion of reaction. However the microwave irradiation took only 3-5 minutes. Even though the reaction rate was faster in microwave condition when compared to classical reaction, the isolation of Schiff's base was somewhat difficult. In classical reaction, the product isolation was performed by simple filtration after completion of reaction. In microwave method, the product isolation was performed first by quenching the reaction mass into chilled water then isolating the product by filtration. Further, the classical reaction did not require any additional purification of Schiff's base, but in the case of microwave condition the isolated Schiff's base needed purification by recrystallization.

Further, the classical reaction gave good yield, but the microwave reaction gave lower yield since it required additional purification to get pure material. In addition to the yield, practical difficulties associated with the isolation of material and drying also played a major role in the filed of synthetic organic chemistry. Hence, isolation and drying in the classical reaction was very easy since it involved organic solvents. But in microwave reaction, it involved isolating the product from solvent containing higher boiling point like water and N,N-dimethylformamide. Removing these solvents from the reaction product was difficult which required high temperature heating.

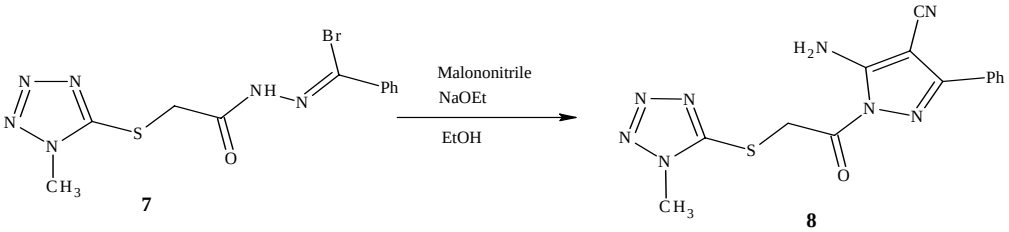
The Schiff's base (**4a**) when reacted with N-bromosuccinimide in N,N-dimethylformamide resulted in the formation of bromo derivative of Schiff's bases (**7**) as represented in **scheme-2**. The reaction was carried out under ice cold temperature by the addition of N-bromosuccinimide into a solution of Schiff's base in N,N-dimethylformamide. The progress of the reaction was monitored by thin layer chromatography using a mixture of chloroform and methanol (7:3) as mobile phase. After completion of the reaction, the reaction was quenched by adding the reaction mixture slowly into ice cold water. The precipitated product was filtered and washed with sufficient water to remove the residual N,N-dimethylformamide and the by-product succinimide. It was dried under vacuum to remove the solvent water.

The bromo derivative of Schiff's bases prepared above on treatment with anion of malononitrile was expected to yield the pyrazole derivative (**8**) as represented in **scheme-3**.



4a **7**

Scheme 2: Synthesis of bromo derivatives of Schiff's base of acylated hydrazine derivatives of mercapto heterocyclic compounds



Scheme 3: Synthesis of pyrazole derivatives from bromo derivatives of Schiff's base of acylated hydrazine derivatives of mercapto heterocyclic compounds

The reaction was monitored by thin layer chromatography using a mixture of chloroform and methanol (7:3) as mobile phase. The expected product was not formed even with the use of potassium tert-butoxide in place of sodium methoxide as a base for the generation of anion of malononitrile.

The probable reason for the failure of this reaction may be due to the behaviour of the bromo derivative of Schiff's base as vinylic bromide rather than allylic bromide.

CONCLUSION

Various Schiff's base derivatives of mercaptoheterocyclic compounds were prepared by condensing acylated hydrazine derivatives of mercapto heterocyclic compounds with various aromatic aldehydes and a comparative study of classical and microwave assisted synthesis of Schiff's bases were also performed. The synthesized compounds were confirmed by various analytical techniques. The possibility to use Schiff's base in the preparation of pyrazole derivative was also explored. The acylated hydrazine derivative (**1-3**) used for the synthesis of Schiff's base were prepared according to the procedure reported in the literature[12].

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