Indian Journal of Chemistry
Vol. 48B, March 2009, pp. 460-466

Note

Microwave-assisted one-pot synthesis of antifungal active 1-substituted-3,7-dialkyl/aryl-4*H*-pyrazolo[4,5-*f*]-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines using solid support

Monika Gupta*, Satya Paul & Rajive Gupta

Department of Chemistry, University of Jammu, Jammu 180 006, India

E-mail: monika.gupta77@indiatimes.com

Received 5 February 2008; accepted (revised) 31 December 2008

A simple, efficient and environment-friendly procedure is developed for the synthesis of 1-substitued-3,7-dialkyl/aryl-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines **3** by condensation of 1-amino-2-mercapto-1,3,4-triazoles **1** and 5-chloro-4-formyl-1,2-pyrazoles **2** in the presence of *N,N*-dimethyl-formamide as an energy transfer medium, *p*-TsOH as catalyst and basic alumina as solid support under microwave irradiation. The products are obtained in good to moderate yields and are in a state of high purity.

Keywords: Pyazolo, triazolo, thiadiazepines, *N,N*-dimethyl-formamide, microwave irradiation

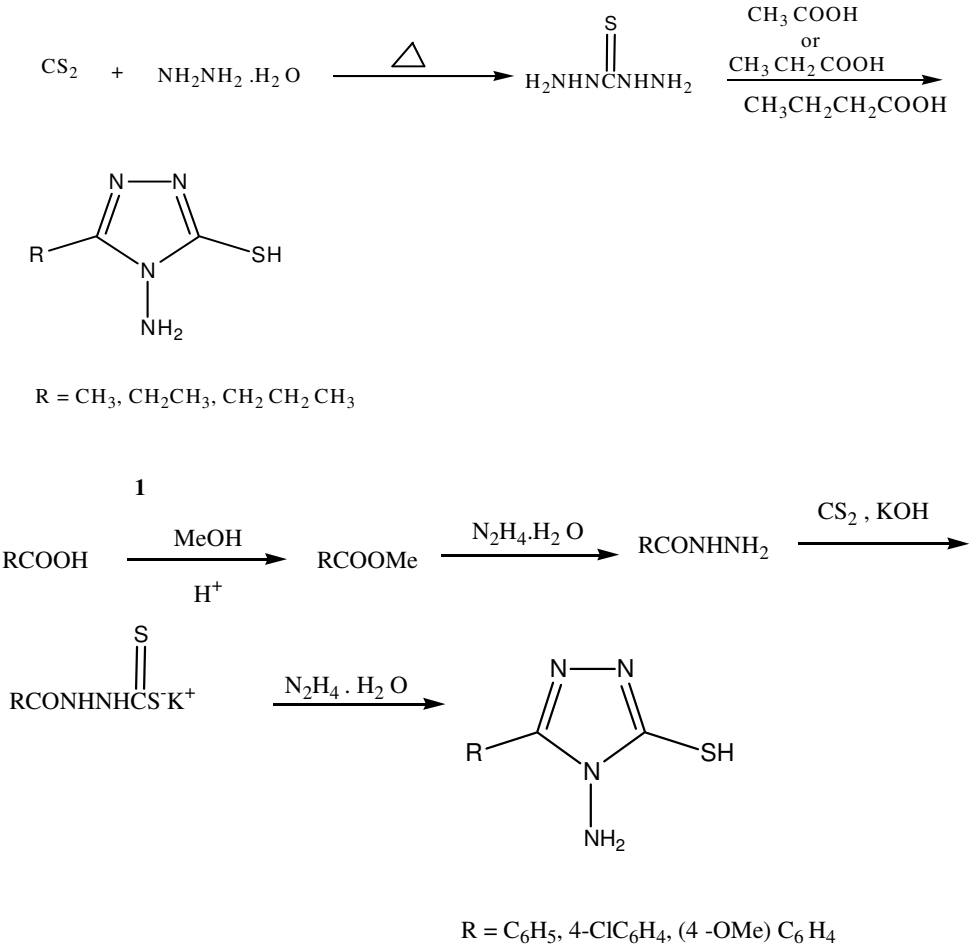
A number of pyrazole derivatives are associated with wide range of biological activities such as antifungal[1], antibacterial[2] etc. Triazole derivatives were known to possess antifungal[2,3], antibacterial[4], antiinflammatory[5], antimicrobial[6,7] and antiasthamatic[8,9] activities while thiadiazepine derivatives were reported to exhibit wide range of biological activities[10] such as herbicidal, antimicrobial, antiinflammatory, analgesics etc. To study the combined effect of these three heterocyclic moieties in a single network, there is a continued interest in the synthesis of 1-substituted-3,7-dialkyl/aryl-4*H*-pyrazolo[4,5-*f*]-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines.

In recent years, microwave activation coupled efficiently with solid supports[11] and present an environment-friendly methodology. Further, work-up procedure is simply reduced to filteration followed by washing with water. Moreover, products are obtained in a state of high purity.

In this paper, an environment-friendly procedure for the synthesis of 1-substituted-3,7-dialkyl/aryl-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines in the presence of *N,N*-dimethylformamide as an energy transfer medium, *p*-TsOH as catalyst and basic alumina as solid support under microwave irradiation is reported.

Results and Discussion

1-Amino-2-mercapto-5-alkyl-1,3,4-triazoles (ref. 12,13) **1**, required for the synthesis of title compounds were prepared from thiocarbohydrazides by heating a mixture of hydrazine hydrate with carbon disulfide and water followed by conversion of the intermediary thiocarbohydrazides[14] to the title compounds by refluxing with gl. AcOH, propionic acid or *n*- butyric acid for 2-5 hr. 1-Amino-2-mercapto-5-aryl-1,3,4-triazoles were prepared from methyl benzoates[15] by treatment with hydrazine hydrate to get aroyl hydrazides[16], which were then converted to potassium salt by stirring with carbon disulfide and potassium hydroxide at RT. Finally, 1-amino-2-mercapto- 5-aryl-1,3,4-triazoles[17] were obtained by refluxing potassium salt with hydrazine hydrate in EtOH for 6-12 hr as shown in **Scheme I**. The other precursor, (3-alkyl/aryl-5-chloro-4-formyl-1,2-pyrazoles)[18], were prepared by Vilsmeir- Haack reaction of pyrazolones/hydrazones as shown in **Scheme II**. The title compounds were then prepared by irradiating a mixture of 1-amino-2-mercapto-1,3,4-triazoles **1**,5-chloro-4-formyl-1,2-pyrazoles **2**, *p*-TsOH, *N,N*-dimethylformamide and basic alumina in a microwave oven at 640 W (**Scheme III**). The role of base catalyzed condensation is to increase the basicity of sulfur atom and provides an environment-friendly procedure. Moreover, inexpensive *p*-TsOH converts carbonyl into good leaving group that increases the rate of reaction. Experimental conditions have been carefully monitored to make the reaction proceed safely and in milder conditions. The amount of reagent used and power level of microwave oven was found to be crucial to proceed the reaction faster and in an environment-friendly way. After carrying out the reaction under different set of conditions, the optimum conditions selected are : for 5 mmole of 1-amino-2-mercapto-1,3,4-triazole **1**, 5 mmole of (5-chloro-4-formyl-1,2-pyrazoles) **2**, 200 mg of *p*-TsOH, 2.5 mmole of *N,N*-dimethylformamide and 1 g of basic alumina was required. A power level of 640 W



Scheme I

was selected as optimum power level. In a test reaction, product **3a** (**Table I**) was obtained in 65% isolated yield, when a mixture of 1-amino-5-methyl -2-mercapto-1,3,4-triazole (5 mmole, 0.655 g), (5-chloro-4-formyl-1,2-pyrazole) (5 mmole, 0.72 g), *p*-TsOH (200 mg), *N,N*-dimethylformamide (2.5 mmole, 0.18 g) and basic alumina (1 g) was irradiated in a microwave oven for 8 min. at 640 W. To check the generality of the reaction, this method was also applied to other substrates and found good to moderate yields.

Antifungal activity

Some of the synthesized compounds were screened for antifungal activity against *Aspergillus flavus, Aspergillus niger, Rhizopus species* and *Pencillium species* by paper disc technique against two concentrations 500 μg/mL and 1000 μg/mL. The zone of inhibition after 24 hr of incubation at 28 ± 2°C was compared with that of standard fluconazole. The screening data indicated that the compounds **3a**, **3c, 3i** and **3j** showed good to moderate activity against *Aspergillus niger, Aspergillus flavus and Rhizopus species* but the tested compounds were inactive against *Pencillium* species at 500 μg as well as 1000 μg concentrations as shown in **Table II**.

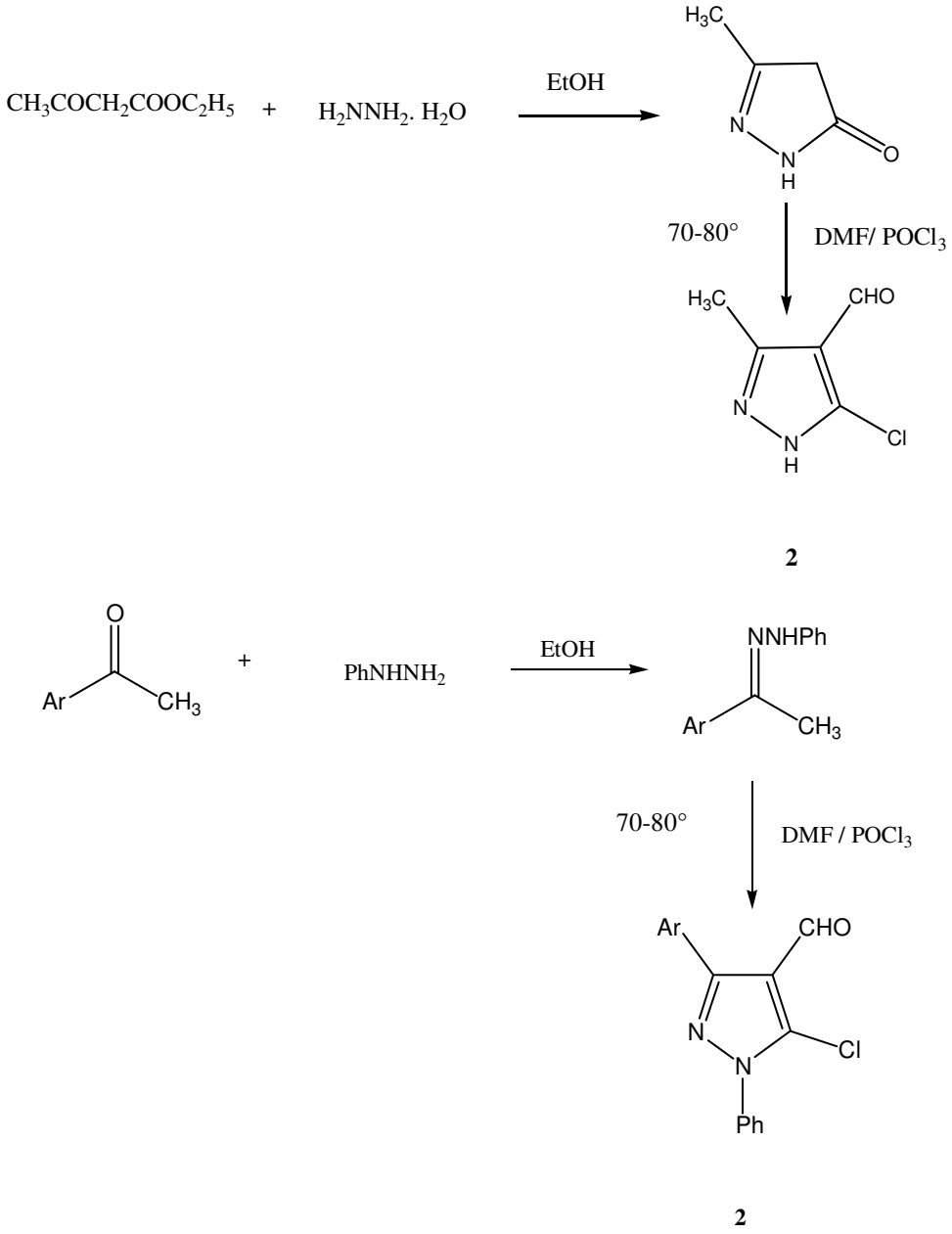
The medium used for evaluation of antifungal activity was potato dextrose agar-agar medium.

Preparation of the medium

Potato dextrose agar-agar medium was prepared as below:

Potato= 250 g, Dextrose= 10 g, Agar-agar= 20 g, Distilled water = 100 mL

Sliced potatoes were taken with 500 mL of distilled water in a pan and boiled for half an hr till a spoon

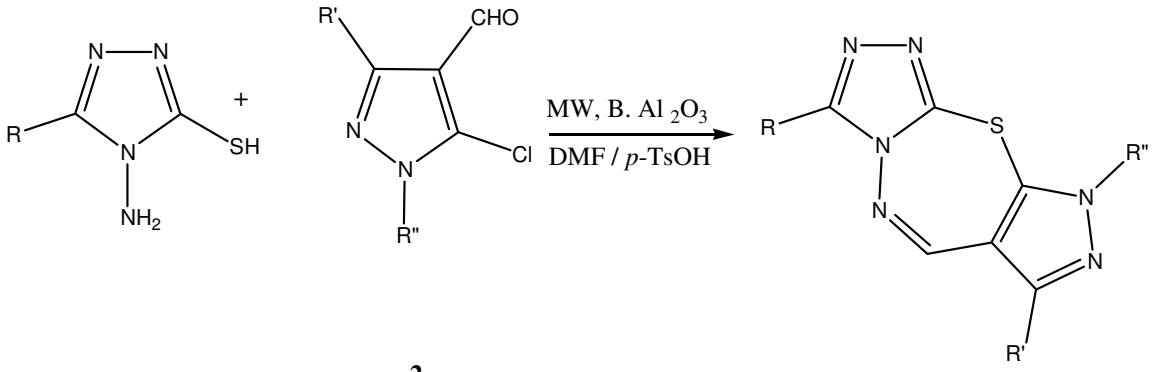


Scheme II

when placed on a slice can pierce into it. Filtered it while hot and broth was again taken in a pan with rest of the distilled water. Dextrose dissolved in distilled water and weighed agar-agar was added to the broth and heated it to boil. The medium thus obtained was sterillized in pressure cooker for 30 min. and few drops of streptomycin were added to prevent it from any bacterial contamination.

Procedure

Potato dextrose medium was prepared and sterilized in pressure cooker for 30 min. Sterillized medium (15 mL) each was pipetted out into flat petridishes. When it solidified 15 mL of warm seeded medium was applied over it. The seeded agar was made by cooling the medium to 40°C and then adding spore suspension to seeded medium. The spores were obtained from ten days culture of *Aspergillus niger, Aspergillus flavus, Pencillium* species and *Rhizopus* species. Before the solidification of agar, the plate was tilted to ensure that coverage should be even. These petridishes were then put into the refrigerator upside down to prevent condensation of moisture. Two concentrations *viz.* 500 and 1000 µg/mL of the



1 **2** **3**

3a: R= CH_3, R′= CH_3, R″= H
3b: R= C_2H_5, R′= CH_3, R″= H
3c: R= *n*-C_3H_7, R′=CH_3, R″=H
3d: R= (4-MeO) C_6H_4, R′=CH_3, R″= H
3e: R= C_6H_5, R′= (4-MeO) C_6H_4, R″= C_6H_5
3f: R= CH_3, R′= (4-NO_2) C_6H_4, R″= C_6H_5
3g: R= *n*-C_3H_7, R′= (4-NO_2) C_6H_4, R″= C_6H_5
3h: R= C_6H_5, R′= 4-BrC_6H_4, R″=C_6H_5
3i: R= (4-MeO)C_6H_4,R′=(4-NO_2)C_6H_4,R″= C_6H_5
3j: R= 4-ClC_6H_4, R′= (4-NO_2) C_6H_4, R″= C_6H_5

Scheme III

Table I — Physical data of compounds **3a-j** (400 W)

Product[a]	Time[b] (min)	Yield[c] (%)	m.p. (°C)
3a[d]	8	65	102-04
3b[d]	9	76	118-20
3c[d]	6	82	148-10
3d[e]	7	74	212-14
3e[d]	7	62	118-20
3f[e]	5	70	231-33
3g[d]	6	75	198-200
3h[d]	16	70	214-16
3i[d]	5	70	162-64
3j[d]	13	69	140-42

[a] Products were characterized by ^{1}H NMR, IR and mass spectral data.
[b]Time was measured by immersing the glass thermometer in reaction mixture by giving a short pulse of 5s followed by 5s cooling time.
[c]Isolated yields.
[d]Products were purified by crystallization from ethylacetate.
[e]Products were purified by passing through a column of alumina and elution with ethyl acetate and petroleum ether.

synthesized compounds were prepared by dissolving the required quantity of compounds in DMF. Sterilized Whatmann filter paper number 541 discs were prepared by cutting 6 mm diameter with a cork borer and were spread individually with a needle and planted upon the chilled seeded medium. The plates were then incubated for 24 to 72 hr at 28°C±2°C and inhibition of zone around each disc was measured from the centre of the discs. The percentage zone of inhibition was calculated by the formula

$$I\% = C\text{-}T/C \times 100$$

Where, I= inhibition
C= diameter of zone of micro- organisms in check
T= diameter of the disc

The zone of inhibition was measured after 24 hr, fluconazole (500 µg/mL and 1000 µg/mL) was used as control standard.

Experimental Section

General. All the melting points were determined on a Perfit melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker DPX-200 NMR spectrometer (200 MHz) in $CDCl_3$ using tetramethyl silane as internal standard and IR spectra was recorded using KBr disc on a Perkin-Elmer FTIR spectrometer. The reactions were monitored by TLC. For the described microwave irradiation , (unmodified) household microwave oven equipped with a turn table was used (LG Smart Chef MS-255R operating at 230V-50Hz having maximum output of 900 W).

General procedure for the synthesis of 1-substituted-8-aryl-3-alkyl/aryl-4*H*-pyrazolo[4,5-*f*][1,2,4]-triazolo[3,4-*b*][1,3,4]thiadiazepines

To a mixture of 1-amino-2-mercapto-1,3,4-triazole **1** (5 mmole), 5-chloro-4-formyl-1,2-pyrazoles **2** (5

Table II — Antifungal activity of compounds **3a, c, i, j** (640 W)

S.No.	Compd Conc. µg/mL	Zone of inhibition (mm%) *Aspergilus niger*		*Aspergillus Flavus*		*Rhizopus Species*		*Pencillium species*	
		500 µg	1000 µg	500 µg	1000 µg	500 µg	1000 µg	500 µg	1000 µg
1	**3a**	22 (36.66)	32 (53.33)	20 (33.33)	24 (40.00)	32 (53.33)	40 (60.66)	06 (10.00)	08 (13.33)
2	**3c**	20 (33.33)	31 (51.66)	21 (35.36)	21 (35.36)	36 (66.66)	39 (65.00)	05 (8.33)	02 (3.33)
3	**3i**	02 (3.33)	14 (23.33)	20 (33.33)	08 (13.33)	28 (46.66)	24 (40.00)	-	-
4	**3j**	08 (13.33)	15 (25.00)	03 (5.00)	09 (15.00)	18 (30.00)	23 (38.33)	-	-

Standard Fluconazole

Aspergillus niger: 500 µg 42 (70.00); 1000 µg 48 (80.00)
Rhizopus species: 500 µg 38 (63.33); 1000 µg 42 (70.00)
Aspergillus flavus: 500 µg 35 (58.33); 1000 µg 42 (70.00)
Pencillium species: 500µg 52 (86.66); 1000 µg 54 (90.00)

mmole) and basic alumina (1 g), *N,N*-dimethylformamide (2.5 mmole) was added. The reaction-mixture was mixed properly with the help of a glass rod and then irradiated in a microwave oven for an appropriate time at 640 W (monitored by TLC, **Table I**). After the completion of reaction, the mixture was extracted with hot *N,N*-dimethylformamide (3 × 15 mL). The solid obtained after pouring of the *N,N*-dimethylformamide extract onto the crushed ice was filtered, washed with water and dried. Finally, the product was obtained in a pure state by crystallization from EtOAc or passing through a column of alumina and elution with ethyl acetate and petroleum ether.

The structures of the synthesized compounds were confirmed by ^{1}H NMR, IR and mass spectral data.

Spectral data of compounds 3a-j

3,7-Dimethyl-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine 3a

This compound was obtained as yellow shining solid (ethyl acetate), m.p. 102-104°C; IR (KBr, cm^{-1}): 3112 (NH), 3010 (aromatic C-H), 2800 (CH_3) , 1608 (C=N) , 1432 (C-N) , 1372 (C-S); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 2.25 (s, 6H, 2 × CH_3), 7.50 (s, C-10H), 8.48 (bs, 1H, NH); ms: *m/z* (M^+): 220.

Anal. Calcd. for $C_8H_8N_6S$: C, 43.63; H, 3.63; N,38.18; S, 14.54. Found: C, 43.60, H, 3.60; N, 38.10; S,14.50%

7-Ethyl-3-methyl-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo-[3,4-*b*][1,3,4]thiadiazepine 3b

This compound was obtained as yellow shining solid (ethyl acetate), m.p. 118-20°C; IR (KBr, cm^{-1}): 3110 (NH), 3010 (aromatic C-H), 2925 (CH_2), 2825 (CH_3), 1610 (C=N), 1414 (C-N), 1372 (C-S); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 1.31-1.33 (t. 3H, -CH_2-CH_3), 2.26 (s, 3H, CH_3), 2.82-2.85 (q, 2H, -CH_2-CH_3), 7.50 (s, C-10H), 8.52 (bs, 1H, NH); ms: *m/z* (M^+): 234.

Anal. Calcd. for $C_9H_{10}N_6S$: C, 48.38; H, 4.83; N, 33.87; S,12.90. Found: C, 48.35; H, 4.80; N, 33.83; S,12.85%.

3-Methyl-4-propyl-4*H*-pyrazolo[4,5-*f*][1,2,4]triazol-[3,4-*b*][1,3,4]thiadiazepine 3c

This compound was obtained as brown shining solid (ethyl acetate), m.p. 148-50°C; IR (KBr, cm^{-1}): 3106 (NH), 3024 (aromatic C-H), 2930 (CH_2), 2806 (CH_3), 1608 (C=N), 1442 (C-N), 1374 (C-S); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 0.95-0.97 (t, 3H, -CH_2-CH_2-CH_3), 1.90-1.92 (m, 2H, -CH_2-CH_2-CH_3), 2.28 (s, 3H, CH_3), 2.80-2.84 (t, 2H, -CH_2-CH_2-CH_3), 7.50 (s, C-10H), 8.50 (bs, 1H, NH); ms: *m/z* (M^+): 248.

Anal. Calcd. for $C_{10}H_{12}N_6S$: C, 48.38; H, 4.83; N, 33.87; S, 12.90. Found: C, 48.35; H, 4.80; N, 33.82; S, 12.88%.

3-Methyl-7-(4′-methoxyphenyl)-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine 3d

This compound was obtained as pale yellow shining solid (ethyl acetate), m.p. 212-14°C; IR (KBr, cm^{-1}): 3152 (NH), 3030 (aromatic C-H), 2810 (CH_3), 1610 (C=N), 1410 (C-N), 1074 (OCH_3), 1372 (C-S); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 2.32 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 7.08-7.22 (m, 2H, H_{arom}), 7.28-7.32 (m, 2H, H_{arom}), 7.50 (s, C-10H), 8.55 (bs, 1H, NH); MS: *m/z* (M^+): 296.

Anal. Calcd. for $C_{14}H_{12}N_6S$: C, 56.75; H, 4.05; N, 28.37; S,1.08. Found: C, 56.72; H,4.02; N, 28.35; S, 1.05%.

***N*-Phenyl-3-(4′-bromophenyl)-7-(4′-chlorophenyl)-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine 3e**

This compound was obtained as pale yellow shining solid (ethyl acetate), m.p. 118-20°C; .IR (KBr, cm^{-1}): 1612 (C=N), 1412 (C-N), 738 (C-Cl), 632 (C-Br); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 7.01- 7.10 (m, 4H, H_{arom}), 7.18-7.22 (m, 4H, H_{arom}), 7.35-7.40 (m, 4H, H_{arom}), 7.51 (s, C-10H); ms: *m/z* (M^+): 532.5

Anal. Calcd. for $C_{24}H_{14}N_6SCl$: C,54.08; H,2.62; N,15.77; S,6.00; Cl,6.66, Br, 14.83. Found: C,54.02; H,2.64; N,15.75; S,5.98; Cl,6.62; Br, 14.80%.

***N*-Phenyl-3-(4′-nitrophenyl)-7-methyl-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine 3f**

This compound was obtained as brown shining solid (ethyl acetate), m.p. 231-33°C; IR (KBr, cm^{-1}): 3120 (NH), 3010 (aromatic C-H), 2802 (CH_3), 1440 (NO_2), 1412 (C-N), 1374 (C-S); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 2.32 (s, 3H, CH_3), 7.05-7.12 (m, 3H, H_{arom}), 7.18-7.22 (m, 2H, Ha_{rom}), 7.60-7.67 (m, 2H, H_{arom} and s, 1H buried C-10H), 8.12-8.20 (m, 2H, H_{arom}); ms: *m/z* (M^+): 403.

Anal. Calcd. for $C_{19}H_{13}N_7O_2S$: C, 56.57; H, 3.22; N, 24.31; O,7.94; S,7.94. Found: C,56.52; H, 3.19; N, 24.28; O,7.90; S,7.90%.

***N*-Phenyl-3-(4′-nitrophenyl)-7-propyl-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine 3g**

This compound was obtained as brown shining solid (ethyl acetate), m.p. 198-200°C; IR (KBr, cm^{-1}): 3100 (NH), 3010 (aromatic C-H), 2928 (CH_2), 2810 (CH_3), 1610 (C=N), 1472 (NO_2), 1414 (C-N), 1412, 1372; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 0.90-0.94 (t, 3H, -CH_2-CH_2-CH_3), 1.89-1.93 (m, 2H, -CH_2-CH_2-CH_3), 2.79-2.83 (t, 2H, -CH_2-CH_2-CH_3), 7.05-7.12 (m, 3H, H_{arom}), 7.18-7.22 (m, 2H, H_{arom}), 7.60-7.62 (m, 2H, H_{arom} and s, 1H buried C-10H), 8.12-8.20 (m, 2H, H_{arom}); ms: *m/z* (M^+): 431.

Anal. Calcd. for $C_{21}H_{17}N_7O_2S$: C, 58.46; H, 3.94; N, 22.73; O, 7.42: S, 7.42. Found: C, 58.41; H, 3.90; N, 22.72; O, 7.38; S, 7.38%.

***N*-Phenyl-3-(4′-bromophenyl)-7-phenyl-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine 3h**

This compound was obtained as pale yellow shining solid (ethyl acetate), m.p. 214-16°C; IR (KBr, cm^{-1}): 3100 (NH), 3001 (aromatic C-H), 1608 (C=N), 1414 (C-N), 1373 (C-S), 57 (C-Br); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 7.08-7.10 (m, 6H, H_{arom}), 7.20-7.28 (m, 6H, H_{arom}), 7.33-7.38 (m, 2H, H_{arom}), 7.52 (s, C-10H); ms: *m/z* (M^+): 498.

Anal. Calcd. for $C_{24}H_{15}N_6BrS$: C, 57.83; H, 3.01; N, 16.86; Br, 15.86; S, 6.42. Found: C, 57.80; H, 2.98; N, 16.82; Br, 15.84; S, 6.40%.

***N*-Phenyl-3-(4′-nitrophenyl)-7-(4′-hydroxyphenyl)-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine 3i**

This compound was obtained as brown shining solid (ethyl acetate), m.p. 162-64°C; IR (KBr, cm^{-1}): 3102 (NH), 3020 (aromatic C-H), 2932 (CH_2), 2800 (CH_3), 1612 (C=N), 1452 (NO_2), 1400 (C-N), 1080 (C-O), 1372 (C-S); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.92 (s, 3H, OCH_3), 7.05-7.12 (m, 3H, H_{arom}), 7.18-7.22 (m, 3H, H_{arom}), 7.60-7.62 (m, 2H, H_{arom} and s, 1H buried C-10H), 8.05-8.12 (m, 2H, H_{arom}); ms: *m/z* (M^+): 483.

Anal. Calcd. for $C_{24}H_{17}N_7O_3S$: C, 59.62;; H, 3.51; N, 20.28; O, 9.93; S, 6.62. Found: C, 59.58; H, 3.49; N, 20.26; O, 9.89; S, 6.60%.

***N*-Phenyl-3-(4′-nitrophenyl)-7-(4′-chlorophenyl)-4*H*-pyrazolo[4,5-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine 3j**

This compound was obtained as brown coloured shinning solid (ethyl acetate), m.p. 140-42°C; IR (KBr, cm^{-1}): 3060 (NH), 3010 (aromatic C-H), 1622 (C=N), 1410 (C-N), 1372 (C-S), 726 (C-Cl); ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 7.08-7.15 (m, 5H, H_{arom}), 7.35-7.50 (m, 3H, H_{arom} and s, 1H buried C-10H), 7.58-7.65 (m, 3H, H_{arom}), 8.10-8.20 (m, 2H, H_{arom}); ms: *m/z* (M^+): 499.5.

Anal. Calcd. for $C_{24}H_{14}N_7O_2ClS$: C, 57.65; H, 2.80; N, 19.61; O, 6.40; Cl, 7.10; S, 6.40. Found: C, 57.62; H, 2.78; N, 19.57; O, 6.36; Cl, 7.06; S, 6.36%.

Acknowledgements

One of the authors (MG) is thankful to the CSIR, New Delhi, for the award of SRF during the period of research.

References

1 Cliford D P, Jackson D P & Edwards K V P, *Pestic Sci*, *7* ,**1976**, 453.
2 Hu C-C, Yan Z, Zhang Zi-Yi, Chun Li Zi & Ren Li, *Indian J Chem,* 29B, **2000**, 791.
3 Udupi R H, Purushottam P & Bhat A R, *Indian J Chem,* 39 B, **2000**, 291.
4 Shafiee A & Tabatabaiee M, *J Chem Eng,* 17, **1998**, 14.
5 Mulwad V V & Pawa R B, *Indian J Chem,* 42B, **2003**, 2901.
6 Kidwai M, Bala S & Mishra A D, *Indian J Chem,* 43 B, **2004**, 2485.
7 Ogura A H & Takahashi I H, *Japan Kokai Tokkyo Koho, Japan Patent* 76, 39, 685, 1977; *Chem Abstr,* 86, **1977**, 5765p.
8 Salerno A, Ceriani V & Perillo I, *J Heterocyclic Chem,* 29, **1992,** 1725.
9 Cherney R J, Duan JJ-W, Voss M E, Chen L-C, Wang DT, Meyer Z R, Wasserman K D, Hardman R-Q, Liu M B, Qian MS, Mandlakar D D, Christ J M, Trazaskos R C, Newton R L, Megolda R R & Decicco C P, *J Med Chem,* 46, **2003,** 1811.
10 Pei Y, Lilly M J, Owen D J, D'Souza L J, Tang X-Q, Nazarbaghi R A, Anderson C M, Glasco S, Eden N J, James I W, Maitra U , Chandrasekaran S, Moos W H & Moos S S, *J Org Chem,* 68, **2003**, 92.
11 (a) Posner G H, *Angew Chem Int Ed Engl*, 17, **1978**, 487; (b) Mc Killop A, Young K W, *Synthesis*, **1979**, 401 & 481; (c) Cornelis A & Laszlo P, *Synthesis,* **1985**, 909; (d) Laszlo P, *Preparative Chemistry Using Supported Reagents*, (Academic Press, Inc., San Diego) **1987**; (e) Smith K, *Solid Supports and* catalysts in organic synthesis, Ellis Harwood, Chichester **1992;** (f) Clark J H, *Catalysis of Organic Reactions by Supported* R*eagents,* (VCH Publishers, Inc., New York), **1994**.
12 Dhaka K S, Mohan J, Chadha V K & Pujari H K, *Indian J Chem,* 12, **1974,** 287.
13 Gakhar H K, Jain A & Gupta S B, *J Indian Chem Soc,* 59, **1982,** 900.
14 Andreith L F & Kipper P S, *J Org Chem, 29,* **1954**, 86.
15 Vogel A I, *Textbook of Practical Organic Chemistry*, 4th Edn, (E. L. B. S and Longman Group Ltd), **1973**, 1215.
16 Agarwal V K, Selveraj R J & Parmar S, *J Med Chem,* 12, **1969,** 324.
17 Heidel J R & Heidel N D, *J Heterocyclic Chem,* 13, **1976,** 925.
18 Kira M A, Abdel-Raeman M O & Gadalla K Z, *Tetrahedron Lett,* 2, **1969**, 109.