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Synthesis and Biological Activities of Some New Series of Azoles†

M.S. HALLUR and S.S. SANGAPURE*
Department of Studies and Research in Chemisry
Gulbarga University, Gulbarga-585 106, India

The reactions of 2-naphthoxy acetate and ethyl salicylate with hydrazine hydrate gave the corresponding hydrazides. Substituted pyrazoles were synthesized by treating the carbohydrazides with ethylacetoacetate, acetylacetone and ethylcyanoacetate. Cyclisation of thiosemicarbazides under appropriate conditions afforded triazole and thiadiazole derivatives. All the compounds were tested for their antimicrobial and antifungal activities.

INTRODUCTION

Compounds containing pyrazole, triazole and thiadiazole ring have been reported to possess antibacterial[1], antifungal[2, 3] and antiinflammatory[4] properties. In an effort to obtain better biologically active compounds, the naphthoxy and salicyl moieties were incorporated into these ring systems.

RESULTS AND DISCUSSION

The condensation of 2-naphthol (**1**) with ethylchloroacetate in anhydrous acetone in presence of anhydrous potassium carbonate at reflux temperature for 10 h gave ethyl 2-naphthoxy acetate (**2**). The structure of compound (**2**) was established on the basis of its IR data and elemental analysis. IR spectra showed absorption band at 1640 cm^{-1} region due to (C=O) group of ester. Hydrolysis of **2** with alcoholic potassium hydroxide yielded 2-naphthoxyacetic acid (**3**) which confirmed the identity of naphthoxy ester (**2**).

Reaction of 2-naphthoxyacetate (**2**) with hydrazine hydrate in ethanol gave 2-naphthoxymethylcarbohydrazide (**5**). The treatment of ethyl salicylate (**4**) with hydrazine hydrate under similar reaction conditions furnished salicyl hydrazide (**6**).

Condensation of 2-naphthoxyacyl/salicylhydrazides (**5** and **6**) with ethylacetoacetate in anhydrous methanol in presence of catalytic amount of hydrochloric acid gave 1-(2-naphthoxyacyl/salicyl)-3-methylpyrazol-5-one (**7, 8**).

The reaction of carbohydrazides (**5, 6**) with acetylacetone in methanol in

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presence of concentrated hydrochloric acid yielded 1-(2-naphthoxyacyl/salicyl)-3,5-dimethylyrazoles (**9, 10**).

Compounds **5** and **6** when reacted with ethylcyanoacetate gave 1-(2-naphthoxyacyl/salicyl)-3-aminopyrazol-5-one (**11, 12**). The structures of all pyrazoles (**7–12**) were established on the basis of spectral data and elemental analysis.

Thiosemicarbazides of 2-naphthoxyacyl hydrazide and salicylhydrazide (**13, 14**) required for the synthesis of triazole and thiadiazole derivatives were obtained by reacting 2-naphthoxymethylcarbohydrazide/salicylhydrazide (**5, 6**) with phenylisothiocyanate in ethanol.

Base catalysed cyclisation of 2-naphthoxyacyl thiosemicarbazide/salicyl-thiosemicarbazides (**13, 14**) led to the formation of 2-(2-naphthoxymethyl/2-hydroxyphenyl)-5-mercapto-1,3,4-triazoles (**15, 16**). Cyclisation of **13** and **14** with orthophosphoric acid furnished 2-(2-naphthoxymethyl/2-hydroxyphenyl)-5-anilino-1,3,4-thiadiazoles (**17, 18**) in good yields.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The IR spectrum was recorded in nujol on a Hitachi 270-50 IR spectrophotometer.

Ethyl-2-naphthoxymethyl acetate (**2**): To a solution of 2-naphthol (0.05 mole) in anhydrous acetone (40 mL) was added ethyl chloroacetate (0.05 mole) and anhydrous potassium carbonate (10 g). The reaction mixture was heated under reflux for 10 h. The potassium salts were filtered off and the filtrate upon removal of acetone furnished colourless solid. It was crystallised from benzene and pet ether as shining needles. Yield 48%, m.p. 52°C. (Found: C, 73.12, H, 6.01; $C_{14}H_{14}O_3$ requires C, 73.04, H, 6.08%)

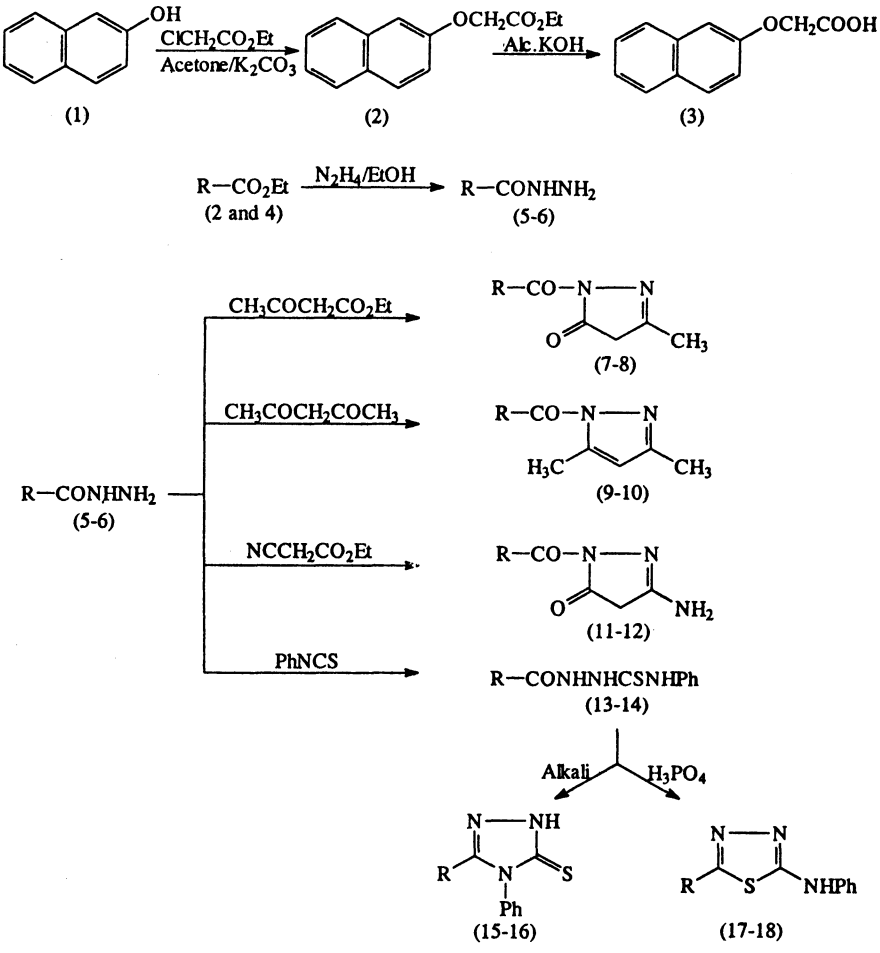
2-Naphthoxyacetic acid (**3**): Ethyl 2-naphthoxyacetate (0.002 mole) was treated with alcoholic KOH and the solution was boiled for few minutes. After cooling few mL of water were added and the solution was acidified with dilute hydrochloric acid. The solid separated was collected and crystallised from ethanol, m.p. 148°C (Lit. m.p. 150–152°C).

2-Naphthoxyacyl/salicylhydrazides (**5, 6**): A mixture of ester (2/4) (0.05 mole), hydrazine hydrate (0.1 mole, 80%) was heated under reflux in ethanol for 5–6 h. The solid separated was collected and crystallised from suitable solvent.

1-(2-Naphthoxyacyl/salicyl)3-methylpyrazol-5-one (**7, 8**): A mixture of carbohydrazide (0.01 mole) and ethylacetoacetate (0.01 mole) was refluxed in anhydrous methanol (10 mL) containing few drops of concentrated hydrochloric acid for 4 h. The resulting solution was concentrated and cooled. The solid separated was collected and crystallised from suitable solvent.

1-(2-Naphthoxyacyl/salicyl)3-5-dimethylpyrazole (**9, 10**): Carbohydrazide (0.01 mole), acetylacetone (0.01 mole) and anhydrous methanol were refluxed together in presence of few drops of concentrated hydrochloric acid for about 4 h. The reaction mixture was concentrated and cooled to room temperature. The solid that separated was collected and crystallised.

1-(2-Naphthoxyacyl/salicyl)-3-aminopyrazol-5-one (**11, 12**): To a mixture of carbohydrazide (0.01 mole) and ethyl cyanoacetate (0.01 mole) in anhydrous


OH
ClCH2CO2Et
Acetone/K2CO3
OCH2CO2Et
Alc.KOH
OCH2COOH
(1)
(2)
(3)
R—CO2Et
(2 and 4)
N2H4/EtOH
R—CONHNH2
(5-6)
R—CONHNH2
(5-6)
CH3COCH2CO2Et
CH3COCH2COCH3
NCCH2CO2Et
PhNCS
R—CO—N——N
O
CH3
(7-8)
H3C
CH3
(9-10)
NH2
(11-12)
R—CONHNHCSNHPh
(13-14)
Alkali
H3PO4
NH
S
Ph
(15-16)
NHPh
(17-18)
For compounds 5, 7, 9, 11, 13, 15 and 17 : R =
OCH2-
For compounds 6, 8, 10, 12, 14, 16 and 18 : R =
OH

SCHEME

methanol (10 mL) were added few drops of concentrated hydrochloric acid. The reaction mixture was heated under reflux for 4 h and worked up as above.

Thiosemicarbazides (**13, 14**): A suspension of carbohydrazides (**5, 6**) (0.01 mole) in super dry ethanol (5 mL) was treated with phenyl isothiocyanate (0.01 mole) and the contents were heated under reflux for 5 h. The semicarbazide separated upon cooling was collected and crystallised.

5-Mercapto-4-phenyl-1-(2-naphthoxymethyl/2-hydroxyphenyl)-1,3,4-triazoles (**15, 16**): Thiosemicarbazide (**13, 14**) (0.005 mole) was heated with aqueous sodium hydroxide (4%, 33 mL) at reflux temperature for 1 h. The clear solution was boiled with activated charcoal, filtered and acidified with acetic acid. The colourless solid that separated was collected and crystallised from suitable solvent.

5-Anilino-2-(2-naphthoxymethyl/2-hydroxyphenyl)-1,3,4-thiadiazole (**17, 18**): Thiosemicarbazide (**13, 14**) (0.005 mole) was added gradually to orthophosphoric acid (20 mL) during 30 min. The reaction mixture was then heated at 120–130°C for 30 min. The resulting slurry was poured into cold water and stirred. The crude solid that separated was collected and crystallised using appropriate solvent.

The melting point, percentage yield and solvent of crystallisation, of compounds (**5–18**) are given in Table-1. IR data of typical compounds is described in Table-2.

TABLE-1
PHYSICAL DATA OF NEW COMPOUNDS

Compound No.	m.p. (°C)	Yield (%)	Solvent of Crystallization	Mol. Formula
5	180	74	Ethanol	$C_{12}H_{12}N_2O_2$
6	148	63	Aqueous ethanol	$C_7H_8N_2O_2$
7	72	40	Pet ether	$C_{16}H_{14}N_2O_3$
8	84	55	Ethanol	$C_{11}H_{10}N_2O_2$
9	64	39	Petroleum ether	$C_{17}H_{16}N_2O_2$
10	64	53	Benzene	$C_{12}H_{12}N_2O_2$
11	50	50	Benzene/pet. ether	$C_{15}H_{12}N_3O_3$
12	104	59	Benzene	$C_{10}H_9N_3O_3$
13	80	58	Benzene	$C_{19}H_{17}N_3OS$
14	181	62	Ethanol	$C_{14}H_{15}N_3OS$
15	287	96	Aqueous ethanol	$C_{19}H_{11}N_3OS$
16	259	96	Ethanol	$C_{14}H_{11}N_3OS$
17	153	65	Ethanol	$C_{17}H_{15}N_3OS$
18	188	74	Benzene	$C_{14}H_{11}N_3OS$

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

TABLE-2
SPECTRAL DATA OF TYPICAL COMPOUNDS

Compound No.	Characteristic absorption bands IR (ujol) cm^{-1}
5	3150, 3240 ν(NH, NH_2) 1640 ν(C=O)
7	1760, 1640 ν(C=O) 1600 ν(C=N)
9	1740 ν(C=O) 1600 ν(C=N)
11	1760, 1640 ν(C=O) 1600 ν(C=N)
13	3450, 3300, 3250 ν(NH, NH) 1680 ν(C=O) 1240 ν(C=S)
15	3450 ν(N—H) 1610 ν(C=N) 1700 ν(C=S)
18	3350 ν(N—H) 1580 ν(C=N)

The compounds were screened for antimicrobial activity against *S. aureus, B. subtilis, E. coli and P. aeruginosa* by cup-plate diffusion method using nutrient agar medium, Gentamycin was used as standard. Salicylthiosemicarbazide **(14)** showed maximum activity against *E. coli* and *P. aeruginosa* whereas all other compounds were moderately active.

The compounds were evaluated for their antifungal activity against *Aspergillus niger* by cup-plate method using nystatin as standard. Compounds **1** and **10** have shown maximum antifungal activity against *A. niger.* 2-naphthoxymethyl-(1-phenyl-5-mercapto)-1,3,4-triazole was moderately active. Other compounds were weakly active.

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