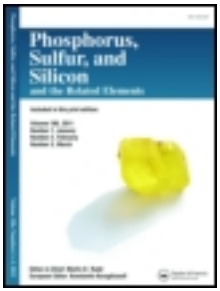

Phosphorus, Sulfur, and Silicon and the Related Elements

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Utility of Hydrazinopiperidinomethanethione in Synthesis of Thiadiazole, Thiadiazine, and Pyrazole Derivatives

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Utility of Hydrazinopiperidinomethanethione in Synthesis of Thiadiazole, Thiadiazine, and Pyrazole Derivatives

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*Hydrazinopiperidinomethanethione **2** was prepared and reacted with active halo compounds, carbon disulfide, phenyliso-thiocyanate, ylidenenitriles, and N,S-acetyls to give thiadiazine **4–7**, thiadiazole **8–10**, and pyrazole **11,13**,**14–17** derivatives, respectively.*

Keywords Hydrazinopiperidinomethanethione; thiadiazine; thiadiazole

INTRODUCTION

Thiadiazoles[1–3] and pyrazoles[4–7] are exhibited a broad spectrum of pharmacological properties such as anti-inflammatory, antiviral, antipyretic, antitumor, and antibacterial. Thiadiazines are also efficient antibacterial and antifungal compounds,[8] and their use in the treatments of the bacterial Helicobacter pylori and as reverse transcriptase inhibitors of the human immunodeficiency virus have been reported.[9,10] Recently,[11] we have used N,N′-diphenylpiperidine-1-carbohydrazonamide in synthesis of pyrazole, triazole, triazine and triazepine derivatives, this prompted us to continue our previous work[5,11] to report here synthesis of thiadiazole, thiadiazine, and pyrazole derivatives via the reaction of hydrazinopiperidinomethanethione **2** with the suitable reagents.

RESULTS AND DISCUSSION

Hydrazinopiperidinomethanethione **2** was prepared by treating 1-piperidinomethanethione **1** with hydrazine hydrate in 1:1 molar ratio,

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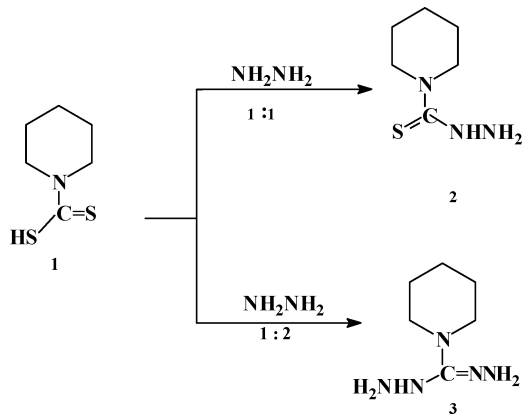


SCHEME 1

while on using 2 mol of hydrazine hydrate, the hydrazinopiperidino-formalhydrazone **3** was obtained. IR spectrum of compound **2** showed absorption peaks at 3463, 3271, and 3194 Cm^{-1}, which corresponded to the presence of NH and NH_2 groups, whereas its ^{1}HNMR showed singlet signal at δ 10.0 for the NH group, broad signal at 6.0–5.4 for the NH_2 group and multiplet signals at 2.4–1.2 for the aliphatic protons (c.f. Scheme 1, Table I).

The reaction of compound **2** with active halo compounds namely; ethyl chloroacetate, chloroacetonitrile, phenacyl bromide, 2,3-dichloro-naphthoquinone, or ethyl chloroformate in the presence of TEA as a basic catalyst, gave the corresponding 2-piperidino-5,6-dihydro-4H-1,3,4-thiadiazin-5-one **4**, 5-amino-2-piperidino-6H-1,3,4-thiadiazine **5**, 5-phenyl-2-piperidino-6H-1,3,4-thiadiazine **6**, 3-piperidino-5,10-dihydro-1H-naphtho[2,3-e][1,3,4]thiadiazine-5,10-dione **7**, and 5-piperidino-2,3-dihydro-1,3,4-thiadiazol-2-one **8**, respectively. The reaction pathway was assumed to proceed via alkylation on the SH group followed by nucleophilic attack of the NH_2 group at CN, CO with elimination of EtOH or H_2O molecule (c.f. Scheme 2, Table I).

Compound **2** was subjected to react with carbon disulfide or phenyl isothicyanate to give the corresponding 5-piperidino-2,3-dihydro-1,3,4-thiadiazole-2-thione **9** and 2(iminophenyl)-5-piperidino-2,3-dihydro-1,3,4-thiadiazole **10**, respectively. IR spectra of compounds **9** and **10** showed the disappearance of the absorption bands corresponding to NH_2 group (c.f. Scheme 3, Table I).

Treatment of compound **2** with ylidenenitriles, namely, *p*-chloro-, *p*-nitro-, or *p*-hydroxybenzylidenemalononitrile, in the presence of TEA as a basic catalyst, gave two products—the first was precipitated

TABLE I Analytical and Spectral Data of the New Compounds 2–17

Product no.	M. P. (°C)[a] cryst. solvent	Yield (%)	Molecular formula (mol. wt.)	Analytical data[b] cal./found C	H	N	S	IR (Cm^{-1})[c]	^{1}H-NMR ∂ (ppm)[d]
2	160–161 ethanol	90	$C_6H_{13}N_3S$ (159.25)	45.25 45.55	8.23 8.47	26.39 26.21	20.10 20.33	3320, 3234, 3160 (NH+NH_2), 1146 (C=S).	10.0 (s, 1H, NH), 5.3–5.0(br, 2H, NH_2), 2.2–2.0 [t, 4H, $N(CH_2)_2$], 1.4–1.0 (m, 6H, $3CH_2$).
3	>300 DMF	93	$C_6H_{15}N_5$ (157.22)	45.84 45.60	9.62 9.90	44.55 44.70		3420,3310,32100, 3170 (NH+$2NH_2$).	8.0(s, 1H, NH),6.5–5.0 (br, 4H, $2NH_2$), 2.2–2.0[t, 4H, $N(CH_2)_2$], 1.4–1.1 (m, 6H, $3CH_2$)
4	185–187 dioxane	66	$C_8H_{13}N_5OS$ (199.27)	48.22 48.43	6.58 6.70	21.09 21.16	16.09 16.22	3172 (NH), 1689 (C=O).	9.2 (s, 1H, NH), 4.2(s, 2H CH_2), 2.3–2.0 [t, 4H, $N(CH_2)_2$], 1.3–1.0(m, 6H, $3CH_2$).
5	221 ethanol	55	$C_8H_{14}N_4S$ (198.28)	48.46 48.60	7.12 7.32	28.26 28.40	16.17 16.33	3334–3254 (NH_2).	6.0 (br, 2H, NH_2), 3.2(s, 2H, CH_2), 2.3–2.0[t, 4H, $N(CH_2)_2$], 1.3–1.0(m, 6H, $3CH_2$)
6	300 dioxane	61	$C_{14}H_{17}N_3S$ (259.36)	64.83 64.60	6.61 6.73	16.20 16.37	12.36 12.55	3012(CH arom.), 1617(C=N).	8.0–7.3(m, 5H, arom.), 3.4(s, 2H, CH_2), 2.3–2.0[t, 4H, $N(CH_2)_2$], 1.3–1.0(m, 6H, $3CH_2$)
7	122 dioxane	91	$C_{16}H_{15}N_3O_2S$ (313.37)	61.33 61.71	4.82 4.60	13.41 13.60	10.23 10.44	3212 (NH), 1660 (2 C=O).	9.0(s, 1H, NH), 8.1–7.3(m, 4H, arom.), 2.3–2.0[t, 4H, $N(CH_2)_2$], 1.3–1.0(m, 6H, $3CH_2$).
8	206–207 ethanol	70	$C_7H_{11}N_3OS$ (185.24)	45.39 45.59	5.99 5.81	22.68 22.50	17.31 17.50	3211 (NH,), 1680 (C=O).	9.4(s, 1H, NH), 2.3–2.0[t, 4H, $N(CH_2)_2$], 1.3–1.0(m, 6H, $3CH_2$).
9	221 toluene	55	$C_7H_{11}N_3S_2$ (201.30)	41.77 41.60	5.51 5.70	20.87 20.60	31.85 31.68	3326 (NH), 1152 (C=S).	9.2(s, 1H, NH), 2.3–2.0[t, 4H, $N(CH_2)_2$], 1.3–1.0(m, 6H, $3CH_2$).
10	280 benzene	69	$C_{13}H_{16}N_4S$ (260.35)	59.97 59.75	6.19 6.23	21.52 21.69	12.31 12.55	3210 (NH), 3050 ($CH_{arom.}$).	9.0(s, 1H, NH),7.5–7.0(m, 5H, arom.), 2.4–2.1[t, 4H, $N(CH_2)_2$], 1.4–1.1(m, 6H, $3CH_2$).
11_a	212 toluene	80	$C_{13}H_{16}ClN_5S$ (281.80)	55.41 55.65	5.72 5.90	14.91 14.80	11.38 11.54	3211(NH), 3059 ($CH_{arom.}$), 1159 (C=S).	10.1(s, 1H, NH), 9.6(s, 1H,=CH), 7.6–7.0(m, 4H, arom.), 2.4–2.1[t, 4H, $N(CH_2)_2$], 1.4–1.1(m, 6H, $3CH_2$)

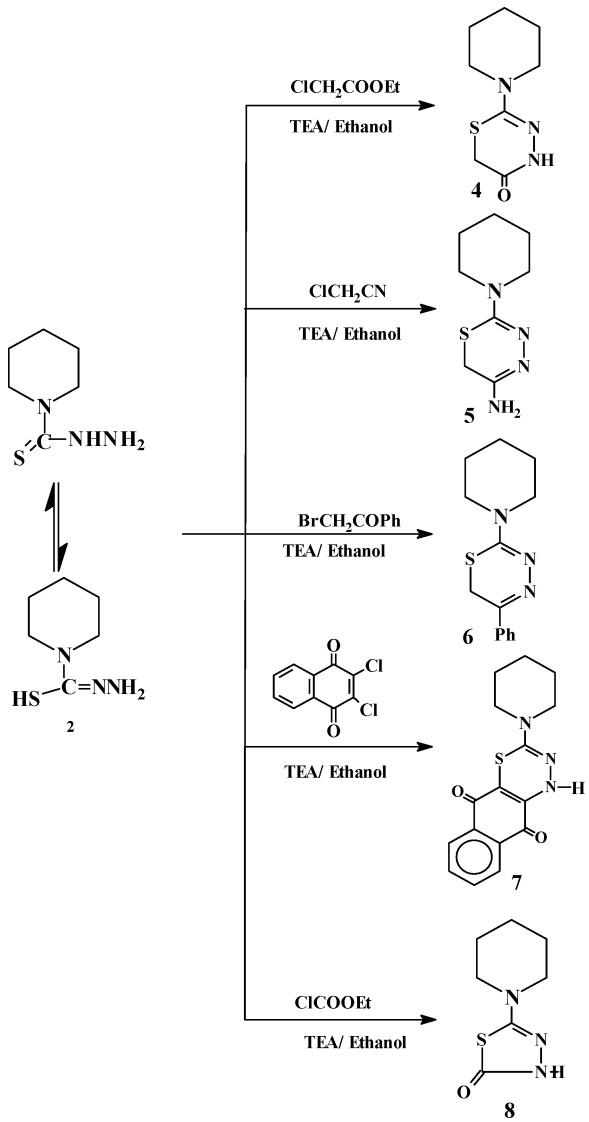
(Continued on next page)

TABLE I Analytical and Spectral Data of the New Compounds 2–17 *(Continued)*

Product no.	M. P. (°C)[a] cryst. solvent	Yield (%)	Molecular formula (mol. wt.)	Analytical data[b] cal./found C	H	N	S	IR (Cm^{-1})[c]	^{1}H-NMR ∂ (ppm)[d]
11$_b$	178 chloroform	30	$C_{13}H_{16}N_4O_2S$ (292.35)	53.41 53.68	5.52 5.70	19.16 19.32	10.97 10.70	3200(NH), 3052 ($CH_{arom.}$), 1150 (C=S).	10.0(s, 1H, NH), 9.0(s,1H, =CH), 7.7–7.0(m, 4H, arom.), 2.4–2.1[t, 4H, $N(CH_2)_2$], 1.4–1.1(m, 6H, $3CH_2$)
11$_c$	283 xylene	75	$C_{13}H_{17}N_3OS$ (263.36)	59.29 59.44	6.51 6.70	15.96 15.80	12.17 12.32	3389(OH), 3208, (NH), 3052 (CH_{arom}), 1150 (C=S).	9.7(s, 1H, NH), 9.0(s, 1H,=CH), 8.0–7.0(m, 4H, arom.), 4.0(s, 1H, OH),2.3–2.0[t, 4H, $N(CH_2)_2$], 1.3–1.0(m, 6H, $3CH_2$).
12$_a$	147 ethanol	77	$C_{16}H_{16}ClN_5S$ (345.85)	55.57 55.70	4.66 4.40	20.25 20.50	9.27 9.43	3281, 3176(NH_2), 2181 (CN).	8.0–7.0(m, 4H, arom.), 6.0–5.3(br, 2H, NH_2), 2.3–2.0[t, 4H, $N(CH_2)_2$], 1.3–1.0(m, 6H, $3CH_2$).
12$_b$	260–262 ethanol	80	$C_{16}H_{16}N_6O_2S$ (356.40)	53.92 53.76	4.52 4.66	23.58 23.60	9.00 9.23	3321, 3214(NH_2), 3051 ($CH_{arom.}$), 2156 (CN), 1550, 1354 (NO_2).	8.0–7.0(m, 4H, arom.), 6.0–5.3 (br, 2H, NH_2), 2.3–2.0[t, 4H, $N(CH_2)_2$], 1.3–1.0(m, 6H, $3CH_2$).
12$_c$	240–241 dioxane	77	$C_{16}H_{17}N_5OS$ (327.40)	58.70 58.90	5.23 5.36	21.39 21.40	9.79 9.90	3400 (OH), 3321, 3214 (NH_2), 3051 ($CH_{arom.}$), 2186 (CN).	8.0–7.0(m,4H,arom.), 6.1–5.6(br,2H,NH_2),3.6(s,1H, OH),2.3–2.0[t,4H,$N(CH_2)_2$], 1.3–1.0(m, 6H, $3CH_2$).
12$_d$	180–181 methanol	79	$C_{16}H_{15}ClN_4OS$ (346.83)	55.41 55.64	4.36 4.43	16.15 16.28	9.24 9.43	3366(OH), 2196 (CN),1160 (C=S).	8.0–7.6(m, 4H, arom.), 3.4 (s, 1H, OH), 2.4–2.1[t, 4H, $N(CH_2)_2$], 1.4–1.1(m, 6H, $3CH_2$).
12$_e$	142 methanol	74	$C_{16}H_{15}N_5O_3S$ (357.38)	53.77 53.50	4.23 4.39	19.60 18.82	8.97 8.70	3374(OH), 2180 (CN), 1550, 1354 (NO_2), 1147 (C=S).	8.0–7.6(m, 4H, arom.), 3.4 (s, 1H, OH), 2.4–2.1[t, 4H, $N(CH_2)_2$], 1.4–1.1(m, 6H, $3CH_2$).

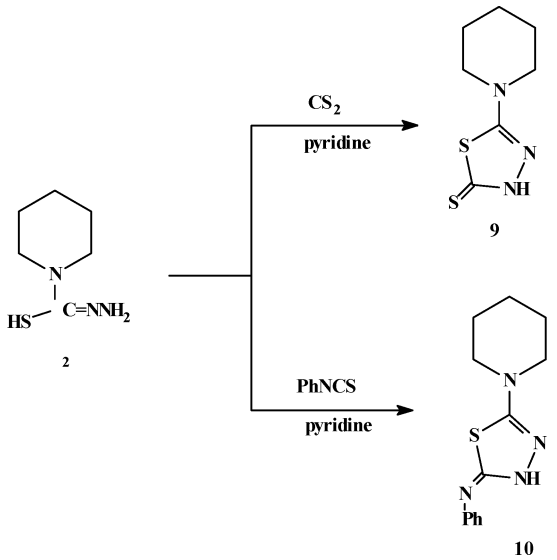
12$_f$	156–158 dioxane	66	$C_{16}H_{16}N_4O_2S$ (328.39)	58.52 58.70	4.91 4.89	17.06 17.19	9.76 9.90	3400, 3378(2OH), 2212 (CN), 1154 (C=S).	8.0–7.6(m, 4H, arom.), 3.4 (s, 1H, OH), 2.4–2.1[t, 4H, $N(CH_2)_2$], 1.4–1.1(m, 7H, $3CH_2$+OH).
13	177–179 xylene	90	$C_{12}H_{21}N_3S$ (239.38)	60.21 60.43	8.84 8.70	17.55 17.61	13.39 13.50	3178(NH), 1148 (C=S).	8.8(s, 1H, NH), 2.4–2.1[m, 8H, $N(CH_2)_2$+ $2CH_2$], 1.8–1.1(m, 12H, $6CH_2$).
14	187–189 dioxane	60	$C_{15}H_{23}N_5S$ (305.44)	58.99 58.70	7.59 7.69	22.93 22.71	10.50 10.42	3344, 3265, 3156 ($NH+NH_2$), 2210 (CN),1140 (C=S).	9.1(s, 1H, NH), 4.0–3.5(br, 2H, NH_2), 2.4–2.1[m, 8H, $N(CH_2)_2$+$2CH_2$], 1.8–1.4(m, 12H, $6CH_2$).
15	211 ethanol	60	$C_{10}H_{13}N_5S$ (235.30)	51.04 51.23	5.57 5.79	29.76 29.89	13.62 13.88	3235,3116 (NH_2), 2212 (CN), 1149 (C=S).	6.6(s, 1H, =CH), 6.0–5.5(br, 2H, NH_2), 2.4–2.1 [m, 4H, $N(CH_2)_2$], 1.8–1.1(m, 6H, $3CH_2$).
16	190–191 methanol	71	$C_{12}H_{18}N_4O_2S$ (282.36)	51.05 51.32	6.43 6.38	19.84 19.81	11.35 11.44	3344,3265 (NH_2), 1708 (C=O), 1154 (C=S).	6.1(s, 1H, =CH), 4.2–3.9(q, 2H, CH_2), 2.4–2.1[m, 4H, $N(CH_2)_2$], 1.8–1.1(m, 9H, $3CH_2$+ CH_3).
17	186 dioxane	66	$C_{16}H_{18}N_6S$ (326.42)	58.87 58.60	5.56 5.77	25.75 25.55	9.82 9.99	3333, 3211, 3145 ($NH+NH_2$), 2210 (CN),1151 (C=S).	8.0–7.0(m, 6H, arom. +NH), 6.0–5.5(br, 2H, NH_2), 2.3–2.0[t, 4H, $N(CH_2)_2$], 1.3–1.0(m, 6H, $3CH_2$).
18	212 dioxane	72	$C_{18}H_{23}N_5O_2S$ (373.47)	57.89 57.67	6.21 6.10	18.75 18.70	8.58 8.80	3311, 3222, 3129 ($NH+NH_2$), 1712 (C=O), 1160 (C=S).	8.0–7.0(m, 6H, arom. +NH), 5.8–5.3(br, 2H, NH_2), 2.3–2.0[t, 4H, $N(CH_2)_2$], 1.3–1.0(m, 6H, $3CH_2$).

[a]Uncorrected; [b]satisfactory microanalysis obtained C; ± 0.35, H; ± 0.40, N; ± 0.30; [c]measured by Nicolet FT-IR 710 spectrophotometer; and [d]measured by a Varian EM 360 L Spectrometer at 60 MHz using TMS as internal standard and DMSO as a solvent.



SCHEME 2

on hot namely Schiff's base $\mathbf{11_{a-c}}$, and the second 5-amino-4-cyano-3-(*p*-chlorophenyl)-1-piperidino-(thioxo)methyl-2,3-dihydro-1H-pyrazole $\mathbf{12_a}$, 5-amino-4-cyano-3-(*p*-nitrophenyl)-1-piperidino(thioxo)methyl-2,3-dihydro-1H-pyrazole $\mathbf{12_b}$ or amino-4-cyano-3-(*p*-hydroxyphenyl)-1-piperidino-(thioxo)methyl-2,3-dihydro-1H-pyrazole $\mathbf{12_c}$ was separated from the filtrate, respectively. Similarly, the reaction of compound **2**



SCHEME 3

with ethyl *p*-chloro-, *p*- nitro – and *p*- hydroxybenzylidenecyanoacetate in the presence of TEA gave a mixture of the Schiff's base $\mathbf{11_{a-c}}$and 4-cyano-5-hydroxy-3-(*p*-chlorophenyl)-1-piperidino(thioxo)methyl-2,3-dihydro-1H-pyrazole $\mathbf{12_d}$, 4-cyano-5-hydroxy-3-(*p*-hydroxyphenyl)-1-piperidino(thioxo)meth-yl-2,3-dihydro-1H-pyrazole $\mathbf{12_e}$, and 4-cyano-5-hydroxy-3-(*p*-nitrophenyl)-1-piperidino-(thioxo)methyl-2,3-dihydro-1H-pyrazole $\mathbf{12_f}$, respectively. Also, on treating compound **2** with *p*-chlorobenzylidenecyanoacetamide in presence of TEA, gave a mixture of compounds $\mathbf{11_a}$ and $\mathbf{12_d}$, respectively. IR spectra of compounds **12** showed the presence of absorption bands corresponding to OH,NH_2groups in addition to CN group at 3400 cm^{-1}, 3320 cm^{-1}, 3200 cm^{-1}, and 2100 cm^{-1}, respectively. ^{1}H-NMR spectra showed the disappearance of the peak corresponding to the SH group and the appearance of the new peak at ~7.00 ppm corresponding to aromatic protons. In analogy, compound **2** was treated with cyclohexylidenemalononitrile and TEA to yield a mixture of the Schiff's base **13** and 2-amino-3-piperidino(thioxo)methyl-3,4-dihydro-spiro[4,5]dec-1-en-1-ylcyanide **14**. The reaction pathway was assumed to proceed via the formation of 1:1 adduct **A**[12], which can loss of active methylene molecule to give Schiff's bases $\mathbf{11_{a-c}}$ and **13** or undergo intermolecular cyclization via a nucleophilic attack of the NH group to the CN or C=O group with elimination of ethanol in case of ethyl arylidenecyanoacetate or ammonia molecule in case of *p*-chlorobenzylidenecyanoacetamide to give products $\mathbf{12_{a-f}}$ and **14**,

respectively. Another route for the synthesis of compounds $\mathbf{12_{a-f}}$ and **14** was achieved by treating the synthesized Schiff's bases $\mathbf{11_{a-c}}$ and **13** with active nitriles in presence of TEA (c.f. Scheme 4, Table I).

It has been reported[13,14] that some substituted hydrazines react with ethoxymethylenemalonmalononitrile or ethyl ethoxymethylenecyanoacetate giving the corresponding pyrazoles, which are potential purine antagonists. In light of these results, it was interest to use compound **2** for preparation of 5-amino-4-cyano-1-piperidino(thioxo)-methyl-1H-pyrazole **15** and 5-hydroxy-4-cyano-1-piperidino(thioxo)-methyl-1H-pyrazole **16** via its reaction with ethoxymethylene-malononitrile or ethoxymethylenecyanoacetate in presence of TEA, respectively. The pathway was assumed to proceed *via* nucleophilic attack of the NH_2 group to the ethylenic bond with elimination of ethanol molecule, followed by another nucleophilic attack of the NH group to the CN group (c.f. Scheme 5, Table I).

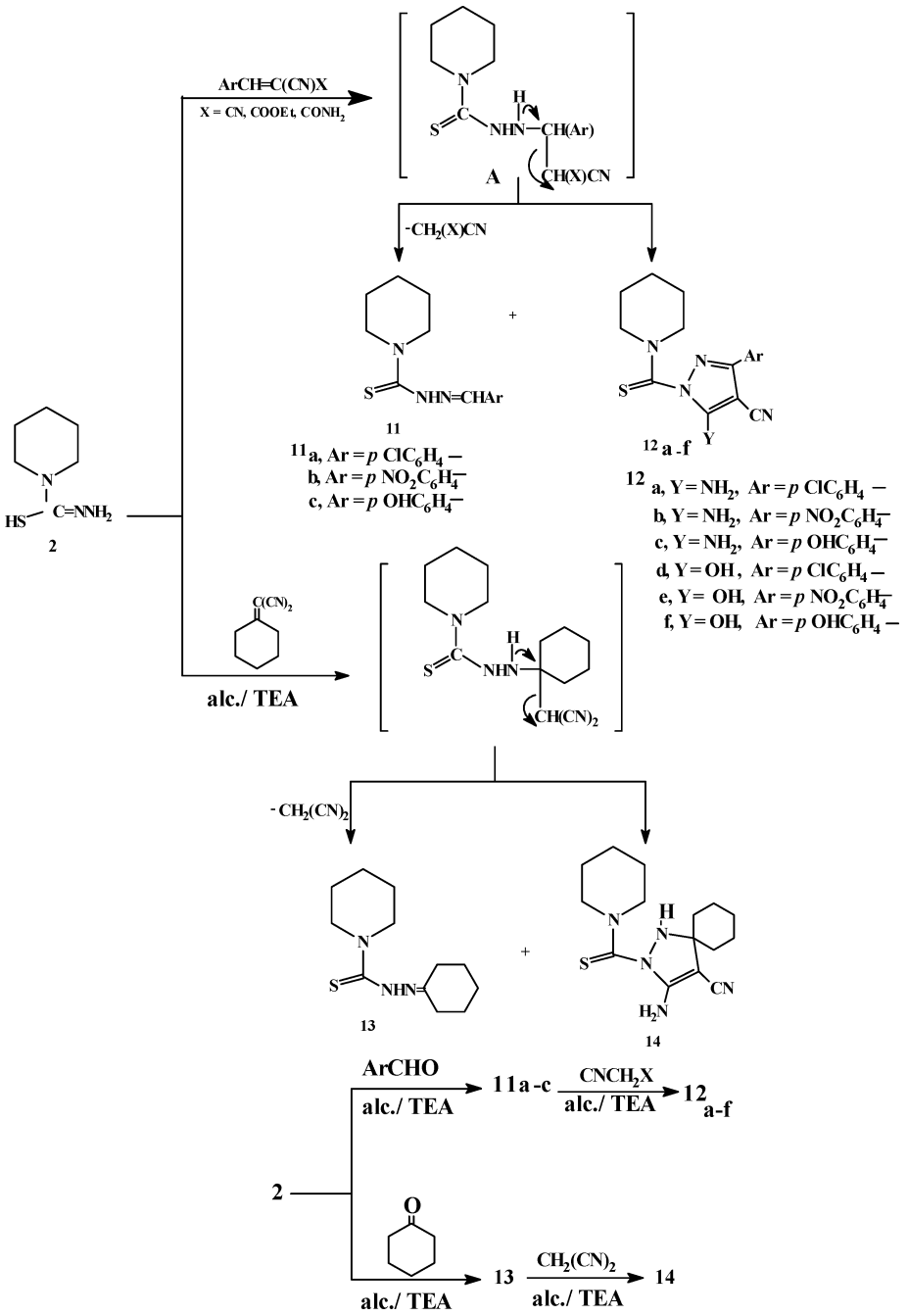
Treatment of compound **2** with (1-methylthio-1′-anilinomethyl-idene)malononitrile or ethyl (1-methylthio-1'-anilinomethylidene)-cyanoacetate in presence of TEA, 5-amino-3-anilino-4-cyano-1-piperidino(thioxo)methyl-1H-pyrazole **17** and 3-anilino-4-cyano-5-hydroxy-1-piperidino(thioxo)methyl-1H-pyrazole **18**, were obtained, respectively. The IR spectra of compounds **15**–**18** showed the presence of the CO group in compounds **16** and **18**. The ^{1}H-NMR spectra are in agreement with the proposed formula. The pathway for the formation of these products was proceeded through nucleophilic attack of the NH_2 group to the ethylenic bond with elimination of MeSH molecule, followed by nucleophilic attack of the NH group to the CN group (c.f. Scheme 5, Table I).

EXPERIMENTAL

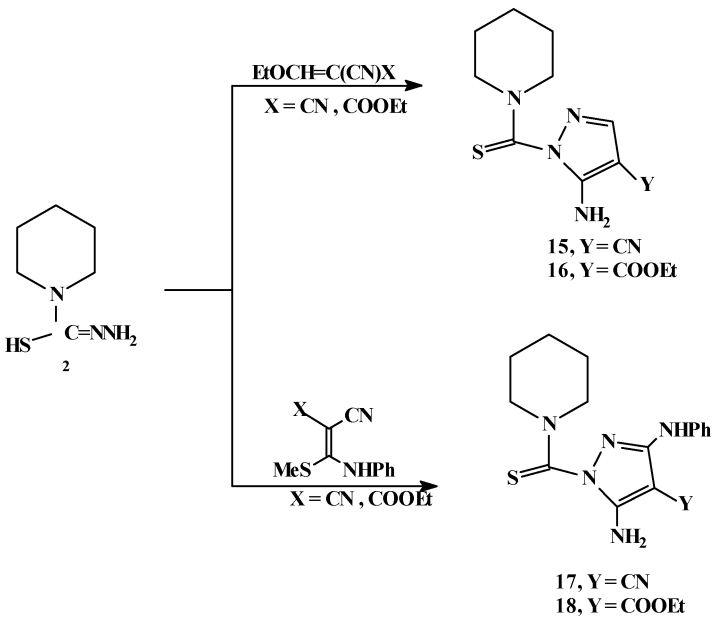
All melting points were determined on a Koffler melting points apparatus and are uncorrected. IR spectra were obtained on a Nicolet 710 FT-IR Spectrometer. ^{1}H-NMR spectra were recorded on a Varian EM 360 at 60 MHz using TMS as an internal reference. Elemental analyses were carried out with an elemental analyzer model 240°C. Satisfactory microanalysis (C $\pm$ 0.4, H $\pm$ 0.4, N $\pm$ 0.3%) were obtained for all newly prepared compounds.

Synthesis of Compound 2

A mixture of 1-piperidinomethanethione **1** (0.01 mol, 1.61 g), hydrazine hydrate (0.01 mol, 0.50 mL) and ethanol (20 mL) was refluxed for 4 h, and the mixture was allowed to cool. The separated solid was collected



SCHEME 4



SCHEME 5

by filtration and recrystallized from ethanol to give **2** (cf. Scheme 1, Table I).

Synthesis of Compound 3

A solution of 1-piperidinomethanethione **1** (0.01 mol, 1.61 g), hydrazine hydrate (0.02 mol, 1.00 mL) in ethanol (20 mL) was refluxed for 10 h. The reaction mixture was filtered on hot, and the precipitant was recrystallized from DMF to give compound **3** (cf. Scheme 1, Table I).

Synthesis of Compounds 4–8

An equimolar ratio (0.01 mol) of compound **2** (1.59 g), halo compound namely; ethyl chloroacetate (1.20 mL), chloroacetonitrile (0.65 mL), phenacyl bromide (1.99 g), 2,3-dichloronaphthoquinone (2.27 g), or ethyl chloroformate (1.10 mL), and TEA (1.41 mL) was refluxed in ethanol (20 mL) for 4 h. The reaction mixture was cooled, and the separated precipitate was filtered off, washed by water, dried, and recrystallized from a suitable solvent to give compounds **4–8**, respectively (cf. Scheme 2, Table I).

Synthesis of Compounds 9 and 10

A solution of compound **2** (0.02 mol, 3.23 g), carbon disulfide (0.02 mol, 1.50 mL) or phenyl isothiocyanate (0.02 mol, 2.81 mL) in pyridine (30 mL) was refluxed for 10 h. After cooling, the reaction mixture was poured into ice-cold water containing drops of HCl. The precipitated solid was filtered off, dried, and recrystallized from a suitable solvent (cf. Scheme 3, Table I).

Synthesis of Compounds $11_{a\text{-}c}$–14 (Method A)

A mixture of 0.01 Mol of compound **2** (1.59 g), arylidinemalononitrile namely; *p*-chloro- (1.88 g), *p*-nitro- (1.99 g), *p*-hydroxybenzylidenemalononitrile (1.71 g), ethyl *p*-chloro- (2.35 g), *p*-nitro- (2.46 g), *p*-hydroxybenzylidenecyanoacetate (2.17 g), *p*-chlorobenzylidenecyanoacetamide (2.06 g), or cyclohexylidenemalononitrile (1.46 mL) and TEA (1.40 mL) in ethanol (30 mL) was refluxed for 3 h. The precipitated solid so formed on hot was filtered off, washed by ethanol, dried, and recrystallized from a suitable solvent to give compounds $\mathbf{11_{a-c}}$ or **13**. The filtrate was evaporated in vacuo. The solid residue was treated with pet. ether 40–60°C and recrystallized to give compounds $\mathbf{12_{a-f}}$ or **14**, respectively (cf. scheme 4, Table I).

Synthesis of Compounds $11_{a\text{-}c}$–14 (Method B)

A solution of an equimolar amount (0.01 mol) of Schiff's base **11a–c** or **13** (0.01 mol) and a selective active nitriles namely malononitrile (0.66 g), ethyl cyanoacetate (1.14 mL) or cyanoacetamide (0.88 g), and TEA (1.50 mL) in dioxane (40 mL) was refluxed for 3 hrs. On cooling, the precipitated solid was filtered off, dried, and recrystallized from a suitable solvent give compounds $\mathbf{12_{a\text{-}f}}$ or **14**, respectively.

Synthesis of Compounds 15–18

0.01 Mol of compound **1** (1.59 g), ethoxymethylenemalononitrile (1.36 g), ethyl ethoxymethylenecyanoacetate (1.83 g), (1-methylthio-1′-anilinomethylidene)malononitrile (4.30 g) or ethyl (1-methylthio-1′-anilinomethyl-idene)cyanoacetate (5.20 g), and triethylamine (1.50 mL) in ethanol (40 mL) was refluxed for 6 h. The reaction mixture cooled and the solid formed was filtered, dried, and recrystallized from a suitable solvent to give compound **15–18**, respectively (cf. Scheme 5, Table I).

REFERENCES

[1] M. Amir, M. S. Y. Khan, and M. S. Zaman, *Indian J. Chem.*, **43,** 2189 (2004).
[2] D. H. Boschelli, D. T. Connor, and T. D. Barnemeier, *J. Med. Chem*., **36,** 1802 (1993).
[3] H. Soad, *Indian J. Chem. Soc.*, **35,** 980 (1996).
[4] N. M. Saleh, Y. A. Ammar, J. A. Micky, H. A. S. Abbas, and M. S. A. EL-Gaby, *Indian J. Chem. Soc*., **43,** 2195 (2004).
[5] Khodairy, A., *Synthetic Comm*., **31,** 2579 (2000).
[6] N. Ram Reddy and P. Pratap Reddy, *Indian J. Chem. Soc.*, **43,** 2165 (2004).
[7] Tisler, M., *Croat. Chem. Acta*, **29,** 409 (1957).
[8] S. A. A. El Bialy, A. M. Abdelal, A. N. El Shorbagi, and M. M. Kheria, *Arch. Pharm. Med. Chem.*, **338,** 38 (2005).
[9] J. C. Costin**,** U.S. Patent, 6, 555, 534 (2003).
[10] M. Witvrouw, M. E. Arranz, C. Pannecouque, R. Declercq, H. Jonckheere, J. C. Schmit, A. M. Vandamme, J. A. Diaz, S. T. Ingate, J. Desmyter, R. Esnouf, L. Van Meervet, S. Vega, J. Balzarini, and E. De Clercq, *Antimicrob. Agents Chemother.*, **42,** 618 (1998).
[11] O. A. Omran, A. A. Amer, and A. Khodairy, *Synthetic Comm.*, **36,** 3647 (2006).
[12] S. A. Osman, G. E. H. El-Gemei, and M. H. El-Nagdi, *Monatsh. Chem*., **117,** 105, (1986).
[13] J. R. Vishnu, *Indian J. of Chem.*, **28B,** 242 (1989).
[14] Z. A. Hozien, F. M. Atta, Kh. M. Hassan, A. A. Abdel-Wahab, and S. A. Ahmed, *Synth. Comm.*, **26,** 3733 (1996).