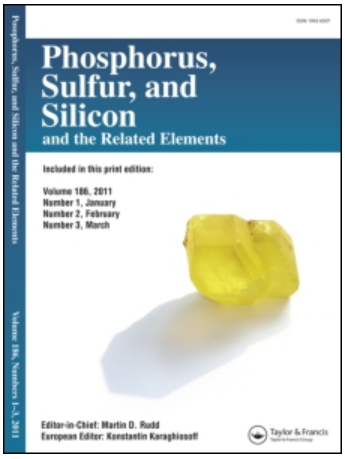

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NEW SYNTHESIS OF IMIDAZO[1,2-a]- AND PYRIMIDO[1,2-a]PYRIMIDINES

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NEW SYNTHESIS OF IMIDAZO[1,2-a]- AND PYRIMIDO[1,2-a]PYRIMIDINES

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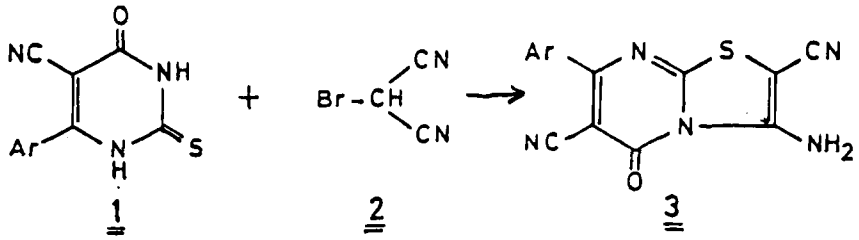
6-Aryl-4-oxo-2- thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitriles (**1**) reacted with bromomalononitrile (**2**) to give 3-amino-7-aryl-5-oxo-5H-thiazolo[3,2-a]pyrimidine-2,6-dicarbonitriles (**3a–c**). The latter compounds reacted with either formic acid, formamide or ammonium thiocyanate to yield the 7-aryl-9-oxo-4-substituted-thiazolo[3,2-a:4,5-d']dipyrimidine-8-carbonitrile derivatives (**4–6**), respectively. Compounds (**3a–c**) could be converted into 7-aryl-3-amino-1-benzyl-5-oxo-5H-imidazo[1,2-a]pyrimidine-6-carbonitriles (**8**) and 4-amino-8-aryl-2,6-dioxo-3-substituted-1,2-dihydro-6H-pyrimido[1,2-a]pyrimidine-7-carbonitriles (**9**) by treatment in boiling ethanol with benzylamine and cyclic secondary amines, respectively.

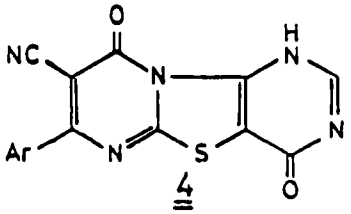
Key words: Imidazo[1,2-a] and pyrimido[1,2-a]pyrimidine.

The use of imidazo[1,2-a]- and pyrimido[1,2-a]-pyrimidine derivatives in medicine is well known.[1–13] The major synthetic approach is to react imidazoleamine or pyrimidineamine with different bifunctional reagents followed by cyclisation of the condensation products.[14–16]

An obvious alternate synthetic route would be the reaction of thiazolo[3,2-a]pyrimidine derivatives with benzylamine and with cyclic secondary amines to get, in one step, imidazo[1,2-a]- and pyrimido[1,2-a]pyrimidine derivatives, respectively. Thus, reaction of 6-aryl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitriles (**1a–c**) with bromomalononitrile (**2**) in aqueous alcoholic potassium carbonate solution gave 3-amino-7-aryl-5-oxo-5H-thiazolo[3,2-a]pyrimidine-2,6-dicarbonitriles (**3a–c**).



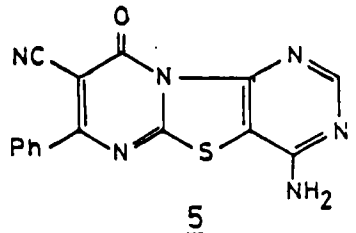
Compounds **3**, as typical enaminonitrile derivatives, reacted with formic acid on heating several hours to yield 7-aryl-4,9-dioxo-1H,4H,9H-thiazolo[3,2-a:4,5-d']-dipyrimidine-8-carbonitriles (**4a–c**).



4

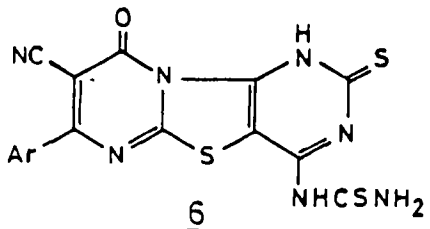
a , Ar = C_6H_5
b , Ar = C_6H_4-Cl-p
c , Ar = C_6H_4-OCH_3-p

Similarly, compound **3a** reacted with formamide in the presence of formic acid and dimethylformamide to yield 4-amino-9-oxo-7-phenyl-9H-thiazolo[3,2-a:4,5-d']-dipyrimidine-8-carbonitrile (**5**).



5

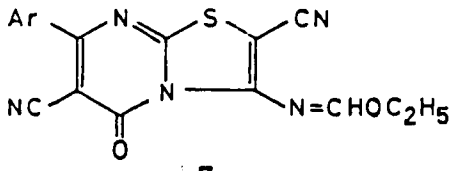
When compounds **3a** and **b** were heated with ammonium thiocyanate in boiling acetic acid, 7-aryl-9-oxo-4-thioureido-2-thioxo-1,2-dihydro-9H-thiazolo[3,2-a:4,5-d']-dipyrimidine-8-carbonitriles (**6a** and **b**) were formed.



6

a , Ar = C_6H_5
b , Ar = C_6H_4-Cl-p

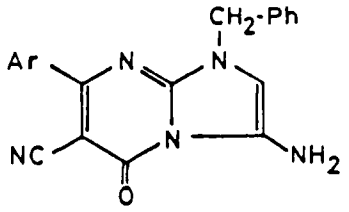
Condensation of (**3a–c**) with triethyl orthoformate in boiling acetic anhydride yielded the corresponding ethoxymethylene derivatives (**7a–c**).



7

a, Ar = C_6H_5
b, Ar = C_6H_4-Cl-p
c , Ar = C_6H_4-OCH_3-p

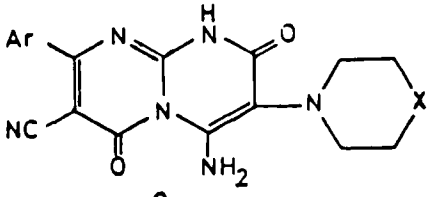
On the other hand, compounds (**3a–c**) suffered ring-opening, hydrolysis of the thiazole nitrile group and decarboxylation as well as recyclisation by elimination of hydrogen sulphide when treated with benzylamine or secondary cyclic amines in boiling ethanol and 3-amino-7-aryl-1-benzyl-5-oxo-5H-imidazo[1,2-a]pyrimidine-6-carbonitriles (**8a–c**) were obtained.



8

a, Ar = C_6H_5
b, Ar = C_6H_4-Cl-p
c, Ar = C_6H_4-OCH_3-p

Reaction of (**3a–c**) with piperidine or morpholine, under the same experimental conditions, led to the formation of 4-amino-8-aryl-2,6-dioxo-3-substituted-1,2-dihydro-6H-H pyrimido[1,2-a]pyrimidine-7-carbonitriles (**9a–f**).



9

a, Ar = C_6H_5 ; X = CH_2
b, Ar = C_6H_5 ; X = O
c, Ar = C_6H_4-Cl-p ; X = CH_2
d, Ar = C_6H_4-Cl-p ; X = O
e, Ar = C_6H_4-OCH_3-p ; X = CH_2
f, Ar = C_6H_4-OCH_3-p ; X = O

EXPERIMENTAL

All melting points are uncorrected—IR spectra were recorded (KBr) on Pye Unicam SP-1000 Spectrophotometer—^{1}H-NMR were obtained with a Varian ^{1}H-Gemini 200 spectrometer and chemical shifts are expressed in δ ppm using TMS as the internal indicator—GCMS-QP 1000 EX mass spectrometer operating at 70 ev. The elementary analyses were performed by Microanalytical Center, Cairo University.

Reactions of (**1a–c**) *with bromomalononitrile:* To a solution of 1 (0.01 mol) in ethanol (25 ml), aqueos solution of K_2CO_3 (0.01 mol in 25 ml of water) and bromomalononitrile (0.01 mol) were added. The reaction mixture was heated at reflux for 1 h, left to cool and poured into water. The solid product so-formed was collected by filtration and crystallized from dilute dimethylfomamide.

3-Amino-5H-5-oxo-7-phenyl-thiazolo[3,2-a]pyrimidine-2,6-dicarbonitrile (**3a**): Yield 2.1 g (71%), m.p. 275°C orange crystals—IR: $\bar{\nu}$ = 3396, 3291 cm^{-1} (NH), 2221, 2203 (CN), 1688 (CO)—^{1}H-NMR (DMSO-d_6): δ = 7.60 (m, 3H, aromatic protons, 7.95 (m, 2H, aromatic protons) and 8.56 (s, 2H, NH_2 exchangeable with D_2O).

$C_{17}H_7N_5OS$ (293.3) Calcd. C 57.33 H 2.39 N 23.89 S 5.46
Found C 57.3 H 2.3 N 23.8 S 5.5

*3-Amino-7-(4-chlorophenyl)-5H-5-oxo-thiazolo[3,2-a]pyrimidine-2,6-dicarbonitrile (***3b***):* Yield 2.3 g (73%), m.p. 299°C, yellow crystals–IR: $\bar{\nu}$ = 3385, 3236 cm^{-1} (NH), 2218, 2210 (CN), 1669 (CO)—^{1}H-NMR (DMSO-d_6): δ = 7.69 (m, 2H, aromatic protons), 8.10 (m, 2H, aromatic protons) and 8.67 (s, 2H, NH_2 exchangeable with D_2O).

$C_{14}H_6ClN_5OS$ (327.7) Calcd. C 51.30 H 1.84 Cl 10.82 N 21.36 S 9.78
Found C 51.3 H 1.8 Cl 10.7 N 21.4 S 9.8

*3-Amino-5H-7-(4-methoxyphenyl)-5-oxo-thiazolo[3,2-a]pyrimidine-2,6-dicarbonitrile (***3c***):* Yield 2.4 g (75%), m.p. 320°C yellow crystals—IR: $\bar{\nu}$ = 3375, 3240 cm^{-1} (NH), 2220, 2210 (CN), 1670 (C)—^{1}H-NMR (DMSO-d_6): δ = 4.10 (s, 3H, OCH_3), 7.53 (m, 2H, aromatic protons), 7.90 (m, 2H, aromatic protons) and 8.83 (s, 2H, NH_2 exchangeable with D_2O).

$C_{15}H_9N_5O_2S$ (323.3) Calcd. C 55.72 H 2.80 N 21.66 S 9.91
Found C 55.7 H 2.8 N 21.7 S 9.9

*Reaction of (***3a–c***) with formic acid:* A mixture of (**3a–c**) (0.01 mol) and formic acid (10 ml) was heated at reflux for 10 h and then left to cool. The solid product so-formed was filtered off and purified by boiling with ethanol several times.

*4,9-Dioxo-7-phenyl-1H,4H,9H, thiazolo[3,2-a:4,5-d']dipyrimidine-8-carbonitrile (***4a***):* Yield 1.9 g (62%), m.p. 340°C, orange crystals—IR: $\bar{\nu}$ = 3295, 3167 cm^{-1} (NH), 2220 (CN), 1699, 1687 (CO)—^{1}H-NMR (DMSO-d_6): δ = 7.60 (m, 3H, aromatic protons), 8.00 (m, 2H, aromatic protons), 8.56 (s, 1H, pyrimidine-H_2) and 11.32 (broad s, 1H, NH exchangeable with D_2O).

$C_{15}H_7N_5O_2S$ (321.3) Calcd. C 56.67 H 2.18 N 21.81 S 9.97
Found C 56.1 H 2.2 N 21.8 S 9.9

*7-(4-Chlorophenyl)-4,9-dioxo-1H-4H,9H-thiazolo[3,2-a:4,5-d']dipyrimidine-8-carbonitrile (***4b***):* Yield 2.2 g (63%), m.p. >350°C yellow crystals—IR: $\bar{\nu}$ = 3310, 3150 cm^{-1} (NH), 2220 (CN), 1699, 1686 (CO)—^{1}H-NMR (DMSO-d_6): δ = 7.73 (m, 2H, aromatic protons), 8.04 (m, 2H, aromatic protons), 8.60 (s, 1H, pyrimidine-H_2) and 11.43 (broad s, 1H, NH, exchangeable with D_2O).

$C_{15}H_6ClN_5O_2S$ (356.5) Calcd. C 50.52 H 1.69 Cl 10.22 N 19.64 S 8.99
Found C 50.5 H 1.7 Cl 10.1 N 19.5 S 8.9

*4,9-Dioxo-7-(4-methoxypenyl)-1H,4H,9H-thiazolo[3,2-a:4,5-d']dipyrimidine-8-carbonitrile (***4c***):* Yield 2.1 g (65%), m.p. >350°C yellow crystals—IR: $\bar{\nu}$ = 3297, 3190 cm^{-1} (NH), 2219 (CN), 1704, 1656 (CO)—^{1}H-NMR (DMSO-d_6): δ = 3.95 (s, 3H, OCH_3), 7.81 (m, 2H, aromatic protons), 8.15 (m, 2H, aromatic protons), 8.55 (s, 1H, pyrimidine-H_2) and 11.25 (broad s, 1H, NH exchangeable with D_2O).

$C_{16}H_9N_5O_2S$ (335.3) Calcd. C 57.31 H 2.69 N 20.89 S 9.55
Found C 57.3 H 2.7 N 20.8 S 9.6

*Reaction of (***3a***) with formamide:* To a mixture of formamid (10 ml), formic acid (5 ml) and dimethylformamide (5 ml), compound **3a** (0.01 mol) was added. The reaction mixture was heated at reflux for 10 h and then left to cool. The solid product so formed was filtered off and purified by boiling with ethanol several times.

*4-Amino-9-oxo-7-phenyl-9H-thiazolo[3,2-a:4,5-d']dipyrimidine-8-carbonitrile (***5***):* Yield 1.8 g (59%), m.p. >350°C yellow crystals—IR: $\bar{\nu}$ = 3380, 3172 cm^{-1} (NH), 2212 (CN), 1696 (CO)—^{1}H-NMR (DMSO-d_6): δ = 7.55 (m, 3H, aromatic protons), 7.70 (m, 2H, aromatic protons), 8.30 (s, 1H, pyrimidine-H_2), 10.20 (broad s, 2H, NH exchangeable with D_2O).

$C_{15}H_8N_6OS$ (320.3) Calcd. C 56.25 H 2.50 N 26.25 S 10.0
Found C 56.3 H 2.5 N 26.3 S 9.8

*Reaction of (***3a,b***) with ammonium thiocyanate:* To a solution of (**3a,b**) (0.01 mol) in acetic acid (20 ml), excess of ammonium thiocyanate (3 g) was added. The reaction mixture was heated under reflux for 6 h, left to cool and poured into water. The solid product was collected by filtration and purified by dissolving in sodium hydroxide solution (50 ml, 2%) and reprecipitated by acidification with hydrochloric acid.

TABLE I

Characterisation data of compounds (8a–c) and (9a–f)

Compound	Molecular Formula	Yield %	M.p. (°C) (Solvent)	Colour	Analysis Calcd. % C % H % N	Found % C % H % N	IR (KBr)
8a	$C_{20}H_{15}N_5O$ (341.3)	63	285 (dilute DMF)	Pale Yellow	70.37 4.42 20.51	70.4 4.4 20.5	3317, 3159 (NH), 2215 (CN), 1670(CO)
8b[a]	$C_{20}H_{14}ClN_5O$ (375.8)	62	318 (dilute DMF)	Colourless	63.92 3.75 18.63	63.9 3.7 18.5	3325, 3156 (NH), 2211 (CN), 1672(CO)
8c	$C_{21}H_{17}N_5O_2$ (371.4)	61	305 (dilute DMF)	Buff	67.91 4.61 18.85	67.9 4.6 18.7	3330, 3167 (NH), 2211 (CN), 1662 (CO)
9a	$C_{19}H_{18}N_6O_2$ (362.3)	70	340 (dilute DMF)	Yellow	62.97 5.01 23.19	62.9 4.8 23.2	3250, 3122 (NH), 2214 (CN), 1660,1655
9b	$C_{18}H_{16}N_6O_3$ (364.3)	70	337 (D M F)	Brown	59.34 4.39 23.08	59.3 4.4 23.1	3253, 3134 (NH), 2208 (CN), 1662, 1655 (CO)
9c[a]	$C_{19}H_{17}ClN_6O_2$ (397.8)	69	>350 (D M F)	Pale Yellow	57.36 4.30 21.12	57.4 4.3 21.1	3315, 3253 (NH), 2211 (CN), 1662, 1656 (CO)
9d[a]	$C_{18}H_{15}ClN_6O_3$ (399.8)	72	>350 (D M F)	Yellow	54.08 3.78 21.02	54.1 3.7 21.1	3253, 3110 (NH), 2210 (CN), 1662, 1656 (CO)
9e	$C_{20}H_{20}N_6O_3$ (392.4)	68	320 (dilute DMF)	Colourless	61.22 5.10 21.43	61.2 5.1 21.4	3242, 3113 (NH), 2215 (CN), 1662, 1589 (CO)
9f	$C_{19}H_{18}N_6O_4$ (394.3)	69	350 (dilute DMF)	Buff	57.87 4.57 21.32	57.8 4.6 21.3	3239, 3107 (NH) 2208 (CN), 1660, 1596 (CO)

[a] 8b. : % Cl, Calcd.: 9.43, Found: 9.4; 9c : % Cl, Calcd.: 8.04, Found: 8.0; 9d : % Cl, Calcd.: 9.12, Found: 9.1

9-Oxo-7-phenyl-4-thioureido-2-thioxo-1,2-dihydro-9H-thiazolo-[3,2-a:4,5-d']dipyrimidine-8-carbonitrile (6a): Yield 3.1 g (76%), m.p. >350°C pale yellow crystals—IR: $\bar{\nu}$ = 3321, 3181 cm^{-1} (NH), 2211 (CN), 1666 (CO)—^{1}H-NMR (DMSO-d_6): δ = 7.67 (m, 3H, aromatic protons), 7.83 (m, 2H, aromatic protons), 8.00 (broad s, 1H, NH exchangeable with D_2O), 8.18 (broad s, 2H, NH_2 exchangeable with D_2O) and 8.78 (broad s, 1H, NH exchangeable with D_2O).

$C_{16}H_9N_7OS_3$ (411.3) Calcd. C 46.72 H 2.19 N 23.84 S 23.35
Found C 46.7 H 2.2 N 23.8 S 23.4

7-(4-Chlorophenyl)-9-oxo-4-thioureido-2-thioxo-1,2-dihydro-9H-thiazolo[3,2-a:4,5-d']dipyrimidine-8-carbonitrile (6b): Yield 3.5 g (79%), m.p. 343°C yellow crystals—IR: $\bar{\nu}$ = 3337, 3186 cm^{-1}

TABLE II
^{1}H-NMR spectra of (**8**) and (**9**)

Compound	^{1}H-NMR (δ Values)
8a[a]	(DMSO-d_6) 4.65 (s, 2H, CH_2), 7.42 (m, 5H, aromatic protons), 7.58 (m, 3H, aromatic protons), 7.88 (m, 3H, 2 aromatic protons and imidazole proton), 11.84 (broad s, 2H, NH_2 exchangeable with D_2O).
8c	($CDCl_3$): δ= 1.60 (s, 2H, NH_2 exchangeable with D_2O), 3.92 (s, 3H, CH_3), 4.80(broad s, 2H, CH_2), 7.00(m, 2H, aromatic protons), 7.30(m, 4H, 3 aromatic protons + imidazole proton),7.48(m, 2H, aromatic protons),8.12 (m, 2H, aromatic protons).
9a	(DMSO-d_6):δ= 1.58 (s, 6H, $3CH_2$), 3.79(s, 4H, $2CH_2$), 7.35(m, 3H, aromatic protons), 7.88(m, 2H, aromatic protons).
9b	($CDCl_3$) : δ= 1.50(s, 2H, NH_2 exchangeable with D_2O), 3.78(m, 4H, 2N-CH_2), 3.90(m, 4H,2 O-CH_2), 7.43(m, 4H, 3 aromatic protons + NH exchangeable with D_2O), 7.90(m, 2H, aromatic protons).
9d	(DMSO-d_6): δ= 3.41(s, 2H, NH_2 exchangeable with D_2O), 3.72(m, 4H, 2N-CH_2), 3.90(m, 4H, 2 O-CH_2), 7.68(d, 2H, aromatic protons), 7.95(d, 2H, aromatic protons).

a) MS (70 eV): m/z (%) = 41 (18.3), 302 (83.6).

(NH), 2225 (CN), 1666 (CO)—^{1}H-NMR (DMSO-d_6): δ = 7.58 (m, 2H, aromatic protons), 7.75 (m, 2H, aromatic protons), 7.92 (broad s, 1H, NH exchangeable with D_2O), 8.10 (broad s, 2H, NH_2 exchangeable with D_2O) and 8.57 (broad s, 1H, NH exchangeable with D_2O).

$C_{16}H_8ClN_7OS_3$ (445.9) Calcd. C 43.09 H 1.81 Cl 7.95 N 21.99 S 21.57
Found C 43.0 H 1.7 Cl 7.9 N 21.8 S 21.6

*Reaction of (**3a–c**) with triethylorthoformate:* To a solution of (**3**) (0.01 mol) in acetic anhydride (20

ml), triethylorthoformate (2 ml) was added. The reaction mixture was heated under reflux for 2 h, and then cooled. The solid product was filtered off and crystallized from dimethylformamide.

*3-Ethoxymethyleneamino-7-phenyl-5-oxo-5H-thiazolo[3,2-a]pyrimidine-2,6-dicarbonitrile (**7a**):* Yield 2.4 g (70%), m.p. 220°C, yellow crystals—IR: $\bar{\nu}$ = 2223, 2214 (CN), 1686 (CO)—^{1}H-NMR ($CDCl_3$): δ = 1.60 (t, 3H, CH_3), 4.45 (q, 2H, CH_2), 7.37 (s, 1H, ethylenic proton), 7.60 (m, 3H, aromatic protons), 8.10 (m, 2H, aromatic protons).

$C_{17}H_{11}N_5O_2S$ (349.3) Calcd. C 58.45 H 3.15 N 20.06 S 9.17
Found C 58.4 H 3.1 N 20.1 S 9.2

*3-Ethoxymethyleneamino-7-(4-chlorophenyl)-5-oxo-5H-thiazolo-[3,2-a]pyrimidine-2,6-dicarbonitrile (**7b**):* Yield 2.7 g (71%), m.p. 245°C, pale yellow crystals—IR: $\bar{\nu}$ = 2223, 2210 (CN), 1704 (CO)—^{1}H-NMR ($CDCl_3$): δ = 1.50 (t, 3H, CH_3), 4.53 (q, 2H, CH_2), 7.32 (s, 1H, ethylenic proton), 7.52 (m, 2H, aromatic protons), 8.04 (m, 2H, aromatic protons).

$C_{17}H_{10}ClN_5O_2S$ (383.8) Calcd. C 53.20 H 2.62 Cl 9.24 N 18.24 S 8.35
Found C 53.2 H 2.5 Cl 9.2 N 18.2 S 8.4

*3-Ethoxymethyleneamino-7-(4-methoxyphenyl)-5-oxo-5H-thiazolo-[3,2-a]pyrimidine-2,6-dicarbonitrile (**7c**):* Yield 2.8 g (74%), m.p. 280°C, orange crystals—IR: $\bar{\nu}$ = 2218, 2210 (CN), 1705 (CO)—^{1}H-NMR ($CDCl_3$): δ = 1.55 (t, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.50 (q, 2H, CH_2), 7.40 (s, 1H, ethylenic proton), 7.83 (m, 2H, aromatic protons), 8.25 (m, 2H, aromatic protons).

$C_{18}H_{13}N_5O_3S$ (379.4) Calcd. C 56.99 H 3.43 N 18.47 S 8.44
Found C 56.9 H 3.4 N 18.5 S 8.4

*Reaction of (**3a–c**) with benzylamine, piperedine and morpholine:* To a solution of (**3a–c**) (0.01 mol) in ethanol (30 ml), benzylamine, piperedine or morpholine (0.01 mol) was added. The reaction mixture was heated under reflux for 5 h, concentrated under reduced pressure and allowed to cool. The solid formed was filtered off and crystallized from the proper solvent to produce (**8a–c**) and (**9a–f**) respectively (Tables I and II).

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