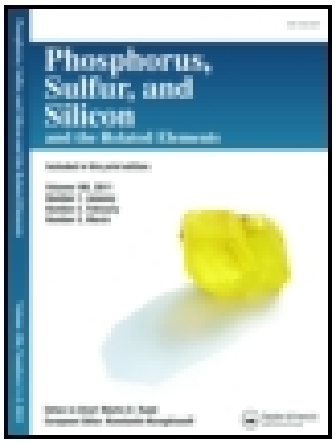

Phosphorus, Sulfur, and Silicon and the Related Elements

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Part 1: Synthesis of Polyfused Heterocyclic Systems Derived From 3-Phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[3,4- b][1,3,4]thiadiazepine-6,8-dione

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PART 1: SYNTHESIS OF POLYFUSED HETEROCYCLIC SYSTEMS DERIVED FROM 3-PHENYL-5,6,7,8-TETRAHYDRO[1,2,4]TRIAZOLO-[3,4-*b*][1,3,4]THIADIAZEPINE-6,8-DIONE

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*3-Phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine-6,8-dione (**1**) was condensed with* o*-aminothiophenol, 2-amino-ethanol or cystamine to afford compounds **2–4** respectively. Treatment of compound **1** with dimethylthiomethylenemalononitrile yielded the corresponding pyrano[3,2-f][1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazepine derivative **5**. 7-[5-Amino-1,3-dithiolan-2-ylidene]-3-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine-6,8-dione (**6**) was obtained by treating compound **1** with CS_2 and chloroacetonitrile. Thiation of compound **1** gave the corresponding thioanalog **7**, which in turn was condensed with malononitrile to give 3-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine-6-one-8-ylidenemalononitrile (**8**). On treating compound **8** with benzaldehyde or* p*-nitrobenzaldehyde, pyrano[1,2,4]triazolo[1,3,4]thiadiazepin derivatives **9a**,**b**, respectively, were obtained. Compound **8** was treated with CS_2 and methyl iodid to give the corresponding dithiomethylmethylene derivative **10** which was subjected to react with aniline to give pyrido[1,2,4]triazolo[1,3,4]thiadiazepine derivative **11**. Compound **8** was treated with 3-aminopyridine,* o*-aminothiophenol, or* o*-phenylenediamene to yield compounds **12** and **13a**,**b** respectively. Finally, tertiary amines or activated phenols were condensed with compound **8** to yield compounds **14** and **15a**,**b** respectively.*

Keywords: CS_2; malonyl dichloride; PTC; thiadiazepine; triazole

INTRODUCTION

It has been reported that free and fused s-triazoles constitute an important class of compounds with a wide biological activities.[1–4] 1,2,4-Triazolo[3,4-*b*][1,3,4]thiadiazole derivatives have anti-bacterial[5,6]

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and anti-inflammatory[7] activities, an interesting CNS depressant action,[8] and moderate anti-malarial and anti-tumor activities.[9] The s-triazolo(3,4-*b*) 1,3,4-thiadiazepines showed significant antimicrobial properties.[10,11] From this view and in the extention of our previous work[12–14] in the synthesis of free and fused s-triazole derivatives, it is reported here in the synthesis of a new series of polyfused 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazepines.

RESULTS AND DISCUSSION

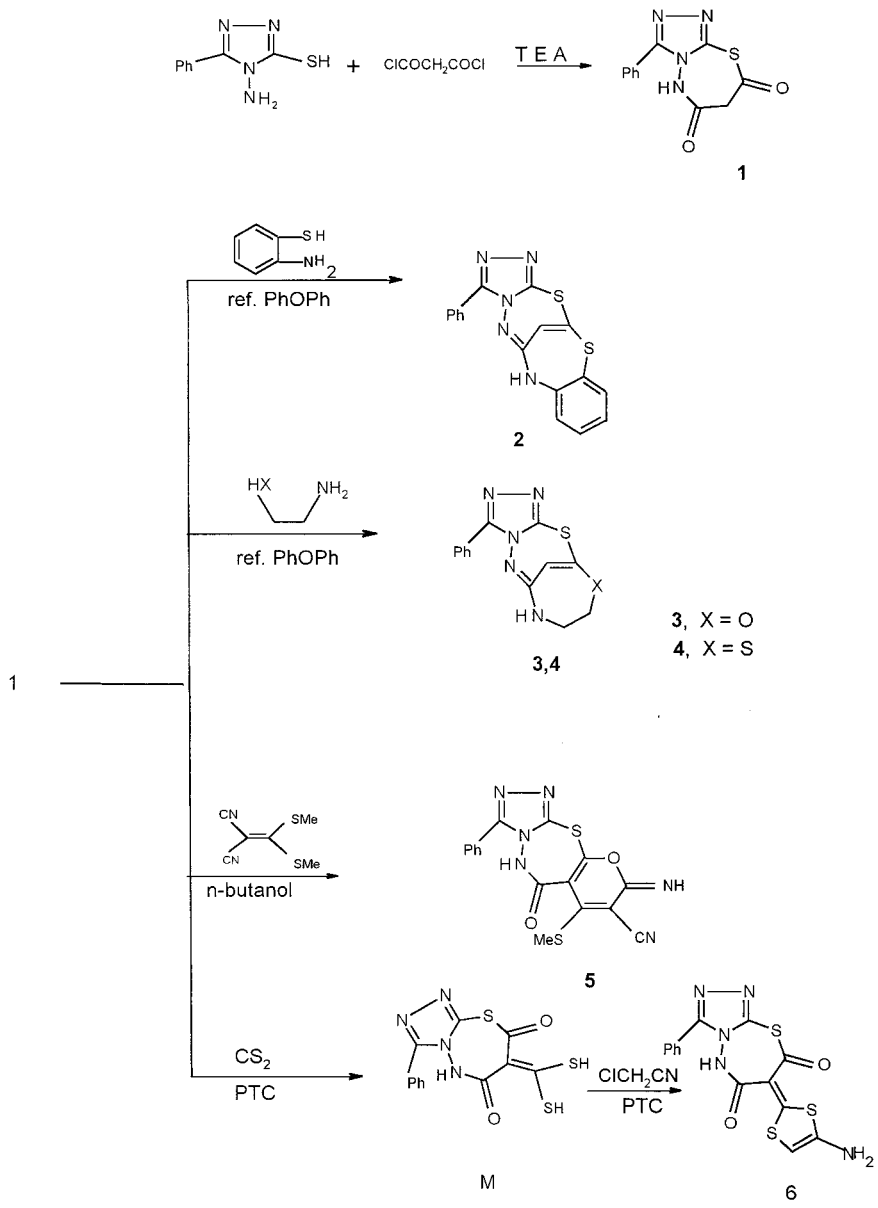
3-Phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine-6,8-dione (**1**) was prepared in a good yield via the reaction of 4-amino-5-phenyl-1,2,4-triazole-3-thione with malonyl dichloride and TEA in 1:1:2 molar ratio at room temperature. The structural assignment of this compound was established by elemental and spectral analyses (Scheme 1, Table I).

Compound **1** was condensed with *o*-aminothiophenol, 2-aminoethanol, or cystamine in refluxing diphenyl ether through intermolecular cyclization with the elimination of two water molecules to give the polyfused derivatives **2–4**, respectively.

Also, compound **1** was reacted in boiling DMF with dimethylthiomethylenemalononitrile, which was prepared via the reaction of malononitrile and CS_2 with two equivalents of methyl iodid in a one-pot reaction using liquid-liquid phase-transfer catalysis (PTC) technique [NaOH/dioxane/tetrabutylammonium bromide (TBAB)], to give 8-cyano-9-imino-7-methylthio-6-oxo-3-phenyl-5,6,8,9-tetrahydro-7*H*-pyrano[3,2-*f*][1,2,4]-triazolo[3,4-*b*][1,3,4]thiadiazepine (**5**) (Scheme 1, Table I).

The 7-[5-amino-1,3-dithiolan-2-ylidene]-3-phenyl-5,6,7,8-tetrahydro [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine-6,8-dione (**6**) was obtained through the intermediate M by treating compound **1** with CS_2 and chloroacetonitrile in one-pot reaction under PTC experimental conditions [DMF/K_2CO_3/TBAB] (Scheme 1, Table I).

Thiation of compound **1** was performed with P_2S_5 in boiling pyridine to give the corresponding thioanalog 3-phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepine-6-oxo-8-thione (7). The IR spectra for this compound showed the absence of a signal corresponding to C=O and the presence of a C=S signal at 1115 cm^{-1} (Scheme 2, Table I). The condensation of compound **7** with malononitrile in boiling DMF gave the dicyanomethylene derivative **8**. The IR and ^{1}H-nmr spectral data are consistent with the proposed structures (Scheme 2, Table I).



SCHEME 1

TABLE I Analytical and Spectral Data of the Prepared Compounds

Comp. no.	m.p.°C[a] (crys. solvent)	Yield (%)	$M_F/(M_w)$	Analytical data calc. (found)[b] % C	H	N	S	IR (KBr) ν (cm^{-1})[c]	^{1}H-NMR (DMSO-d_6)[d] δ (ppm)
1	240 dioxane	79	$C_{11}H_8N_4SO_2$ (260.29)	50.76 50.80	3.10 3.12	21.53 21.50	12.32 12.33	3432 (NH); 3060, 2920 (CH); 1708, 1635 (2C=O)	7.20 (s, 1H, NH); 7.15–6.65 (m, 5H, arom.); 2.97 (s, 2H, CH_2)
2	162 DMF/H_2O	61	$C_{17}H_{11}N_5S_2$ (349.45)	58.43 58.52	3.18 3.15	20.04 20.14	18.35 18.40	3340 (NH); 3050 (CH); 1620 (C=N)	8.20 (s, 1H, NH); 8.00–6.30 (m, 9H, arom.); 6.20 (s, 1H, CH)
3	198–200 DMF/H_2O	55	$C_{13}H_{11}N_5SO$ (285.33)	54.72 54.85	54.72 54.76	24.55 24.38	11.24 11.31	3434 (NH); 3150, 2937 (CH); 1636 (C=N)	7.32 (s, 1H, NH); 7.10–6.45 (m, 5H, arom.); 6.40 (s, 1H, CH); 4.11–3.91 (t, 2H, CH_2); 2.79–2.20 (t, 2H, CH_2)
4	>300 DMF/H_2O	51	$C_{13}H_{11}N_5S_2$ (301.39)	51.81 52.00	3.68 3.75	23.24 23.30	21.28 21.39	3440 (NH); 3140, 2920 (CH); 1620 (C=N)	7.82–6.90 (m, 5H, arom.); 6.11 (s, 1H, CH); 5 (s, 1H, NH); 3.89–3.71 (t, 2H, CH_2); 2.85–2.51 (t, 2H, CH_2)
5	Dec 300 n-butanol	59	$C_{16}H_{10}N_6S_2O_2$ (366.42)	52.45 52.65	2.75 2.88	22.94 22.90	17.50 17.39	3438, 3320 (2NH); 3150, 2954 (CH); 2208 (CN); 1648 (C=O); 1560 (C=N)	7.85–7.00 (m, 5H, arom.); 4.08–3.82 (br, 2H, 2NH); 2.91 (s, 3H, CH_3)
6	160 DMF/H_2O	49	$C_{14}H_9N_5S_3O_2$ (287.47)	16.71 16.53	3.16 3.27	24.36 24.48	33.46 33.41	3422, 3340 (NH_2); 3250 (NH); 3050, 2910 (CH); 1700 (C=O); 1632 (C=N)	8.00 (s, 1H, NH); 7.72–7.00 (m, 5H, arom.); 5.00–4.81 (br, 2H, NH_2); 3.73 (s, 1H, CH)
7	280 Pyridine/H_2O	73	$C_{11}H_8N_4S_2O$ (276.34)	47.81 47.92	2.92 3.00	20.27 20.39	23.21 23.32	3422 (NH); 3060, 2910 (CH); 1647 (C=O); 1060 (C=S)	7.51 (s, 1H, NH); 7.40–6.32 (m, 5H, arom.); 2.24 (s, 2H, CH_2)

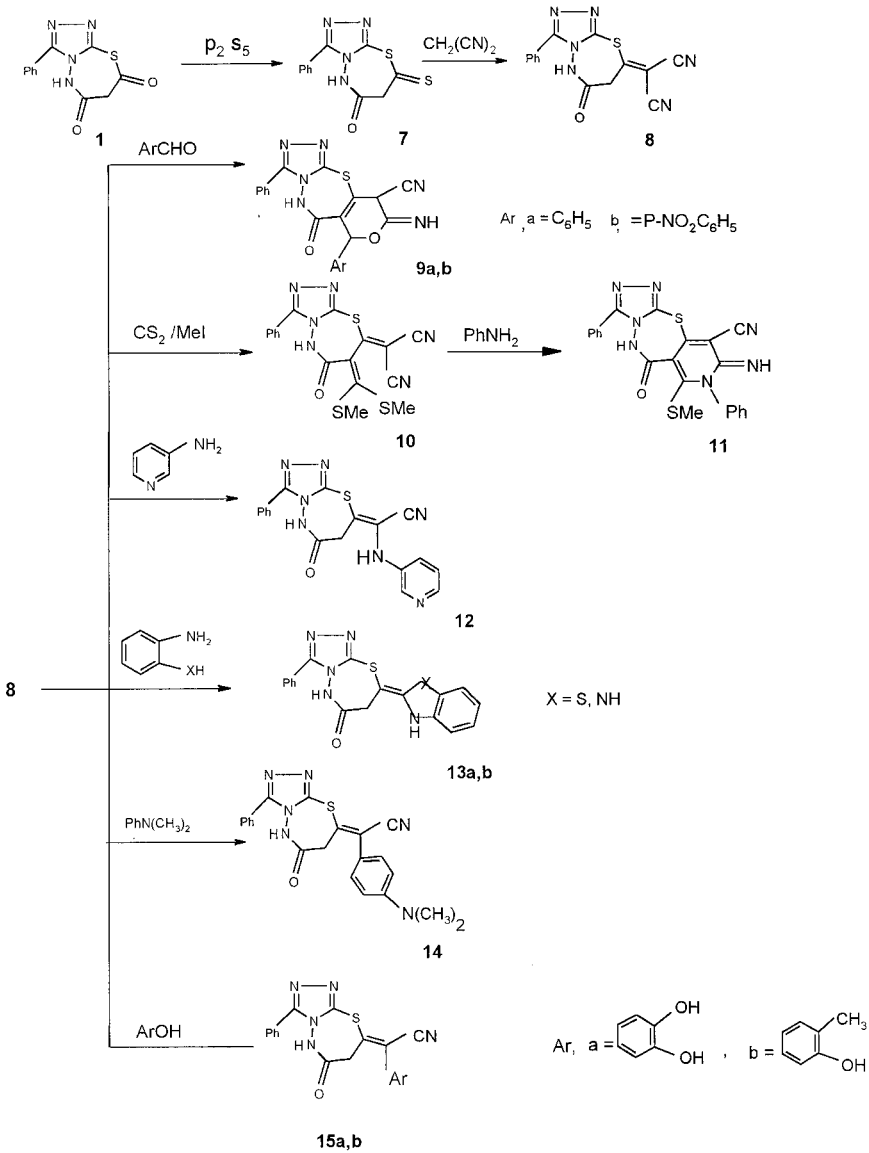
8	>300 DMF/H_2O	68	$C_{14}H_8N_6SO$ (308.32)	54.54 54.70	2.62 2.60	27.26 27.19	10.40 10.49	3312 (NH); 3185, 2926 (CH); 2199, 2128 (2CN); 1641 (C=O)	7.30 (s, 1H, NH); 7.15–6.40 (m, 5H, arom); 2.66 (s, 2H, CH_2)
9a	>300 DMF/H_2O	63	$C_{21}H_{14}N_6SO_2$ (414.45)	60.86 60.99	3.41 3.50	20.28 20.18	7.74 7.80	3407, 3210 (2NH); 3060, 2928 (CH); 2203 (CN); 1620 (C=O).	7.40 (s, 1H, NH); 7.36–6.32 (m, 10H, arom.); 3.39 (s, 1H, NH); 2.66 (s, 1H, CH); 2.25 (s, 1H, CI)
9b	>300 DMF/H_2O	72	$C_{21}H_{13}N_7SO_4$ (459.45)	54.90 54.79	2.85 3.00	21.34 21.25	6.98 6.89	3421, 3225 (2NH); 3030, 2926 (CH); 2204 (CN); 1621 (C=O); 1530, 1350 (NO_2)	8.49 (s, 1H, NH); 8.12–7.00 (m, 9H, arom.); 4.30 (s, 1H, NH); 2.60 (s, 1H, CH); 2.42 (s, 1H, CH)
10	>300 DMF/H_2O	50	$C_{17}H_{12}N_6S_3O$ (412.52)	49.50 49.61	2.93 3.10	20.37 20.31	23.32 23.40	3429 (NH); 3085, 2930 (CH); 2200 (CN); 1653 (C=O)	7.41–6.80 (m, 5H, arom.); 3.00 (s, 1H, NH); 2.83 (s, 3H, CH_3); 2.68 (s, 3H, CH_3)
11	>300 DMF/H_2O	39	$C_{22}H_{15}N_7S_2O$ (457.54)	57.75 57.74	3.30 3.30	21.43 21.50	14.02 14.00	3417, 3220 (2NH); 3050, 2927 (CH); 2205 (CN); 1620 (C=O)	7.82 (s, 1H, NH); 7.70–6.31 (m, 10H, arom.); 2.85 (s, 1H, NH); 2.41 (s, 3H, CH_3)
12	Dec 300 DMF/H_2O	83	$C_{18}H_{13}N_7SO$ (375.42)	57.74 57.90	3.49 3.35	26.19 26.02	8.56 8.47	3426, 3230 (2NH); 3045, 2928 (CH); 2201 (CN); 1631 (C=O)	8.69–8.00 (m, 4H, heterocyclic); 7.51 (s, 2H, 2NH); 7.31–6.32 (m, 5H, arom.); 2.55 (s, 2H, CH_2)
13a	>300 DMF/H_2O	75	$C_{18}H_{13}N_5OS2$ (379.47)	56.97 57.13	3.45 3.54	18.46 18.40	16.90 17.00	3441, 3250 (2NH); 3030, 2910 (CH); 1632 (C=O)	7.42 (s, 1H, NH); 7.35–5.20 (m, 9H, arom.); 2.32 (s, 2H, CH_2); 2.15 (s, 1H, NH)

(*Continued on next page*)

TABLE I Analytical and Spectral Data of the Prepared Compounds *(Continued)*

Comp. no.	m.p.°C[a] (crys. solvent)	Yield (%)	$M_F/(M_w)$	Analytical data calc. (found)[b] % C	H	N	S	IR (KBr) ν (cm^{-1})[c]	^{1}H-NMR (DMSO-d_6)[d] δ (ppm)
13b	Dec 300 DMF/H_2O	71	$C_{18}H_{14}N_6SO$ (362.42)	59.65 59.78	3.89 4.00	23.19 23.12	8.84 8.76	3441, 3250 (3NH); 3010, 2930 (CH); 1640 (C=O)	7.94 (s, 1H, NH); 7.78 (s, 2H, 2NH); 7.41–6.20 (m, 9H, arom.); 2.38 (s, 2H, CH_2)
14	>300 DMF/H_2O	60	$C_{21}H_{18}N_6SO$ (402.48)	62.67 62.48	4.51 4.61	20.88 20.79	7.97 7.83	3425 (NH); 3040, 2905 (CH); 2200 (CN); 1632 (C=O)	7.68 (s, 1H, NH); 7.40–6.15 (m, 9H, arom.); 2.40 (s, 2H, CH_2); 2.20 (s, 6H, $2CH_3$)
15a	>300 DMF/H_2O	69	$C_{19}H_{13}N_5SO_3$ (632.73)	36.07 36.26	2.07 2.20	11.07 11.15	5.07 5.20	3550 (20H); 3434 (NH); 3060, 2905 (CH); 2204 (CN); 1639 (C=O)	8.30 (NH); 8.00–6.67 (m, 8H, arom.); 3.65 (s, 1H, OH); 2.82 (s, 2H, CH_2); 2.15 (s, 1H, OH)
15b	>300 DMF/H_2O	62	$C_{20}H_{15}N_5SO_2$ (389.44)	61.68 61.80	3.88 3.95	17.98 17.90	8.23 8.39	3430 (NH); 3030, 2910 (CH); 2200 (CN); 1640 (C=O)	8.00 (s, 1H, NH); 7.32–6.31 (m, 8H, arom.); 2.56 (s, 2H, CH_2); 1.91 (s, 3H, CH_3); 1.10 (s, 1H, OH)

[a] Uncorrected.
[b] Satisfactory microanalyses; obtained; C, ±0.35%; H, ±0.11%; N, ±0.40%; S, ±0.21%.
[c] Measured on Nicolet 710 FT-IR spectrophotometer.
[d] Measured with a Varian EM 360L spectrometer at 60 MHz using TMS as internal standard.



SCHEME 2

Compound **8** was allowed to react with benzaldehyde or *p*-nitrobenzaldehyde to afford the corresponding 10-cyano-9-imino-6-oxo-3-phenyl-7-phenyl(*p*-nitrophenyl)-5,6,9,10-tetrahydro-7*H*-pyrano[3,4-*f*]-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazepines (**9a**,**b**) respectively. The

reaction mechanism was postulated to proceed through the nucleophilic attack of the active CH_2 group of compound **8** at the carbonyl group of the aromatic aldehyde producing the corresponding aldol adduct, followed by intramolecular cyclization via the nucleophilic addition of the formed OH group at the CN group. The IR spectra of compounds **9a**,**b** showed the absence of a band corresponding to one CN group and the presence of the adsorption bands corresponding to =NH, CN and $C{=}O_{amidic}$ groups at 3421, 2204 and 1650 cm^{-1}, respectively (Scheme 2, Table I).

Compound **8** was treated with an equimolar ratio of CS_2 and double molarity of methyl iodide to yield the corresponding s-methyl derivative **10**; the latter, in turn, underwent cyclization when treated with aniline in 1:1 or 1:2 molar ratio, affording 3,8-diphenyl-5,6,7,8,9,10-hexahydropyrido-9-imino-7-methylthio-6-oxo[3,4-*f*][1,2,4]triazolo[3,4-*b*][1,3,4]-thiadiazepine (**11**).

The behaviour of compound **8** toward amines and phenols was investigated. The products resulted from initial attack of the nucleophile at the C-α of the dicyanomethylene moiety.[15] Thus, compound **8** was condensed with 3-aminopyridine in a 1:3 molar ratio through the hydrogen cyanide elimination to yield the condensed product **12**. Also treatment of compound **8** with *o*-aminothiophenol or *o*-phenylenediamine in refluxing DMF yielded the cyclized products **13a**,**b** via elimination of two HCN molecules. Moreover, compound **8** was allowed to react with *N*,*N*-dimethylaniline or activated phenols, namely resorcinol or *o*-cresol, to furnish the desired compounds **14** or **15a**,**b** respectively.

The structures of all products were established by using elemental and spectral analyses.

EXPERIMENTAL

Synthesis of 3-Phenyl-5,6,7,8-tetrahydro[1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazepine-6,8-dione (1)

To a solution of 4-amino-5-phenyl-1,2,4-triazole-3-thione (0.01 mol) in dry *p*-xylene (30 ml) were added triethylamine (0.02 mol) and malonyl dichloride (0.01 mol) dropwise. The reaction mixture was stirred for 8 h at room temperature. The reaction mixture was then filtered off, dried, and washed with water. The precipitate was dried and crystallized from dioxane (Table I).

Synthesis of Compounds 2–4

General Procedure

To a solution of compound **1** (0.01 mol) in diphenyl ether (15 ml), was added *o*-aminothiophenol, 2-aminoethanol, or cystamine (0.01 mol). The reaction mixture was refluxed for 3 h, concentrated, and cooled. The precipitate was filtered off and crystallized from suitable solvent (Table I).

Synthesis of Compound 5

A mixture of compound **1** (0.005 mol) and dimethylthiomethylene malononitrile (0.005 mol) was refluxed in *n*-butanol (15 ml) untill elimination of MeSH ceased ($\simeq$10 h). The reaction mixture was concentrated and cooled. The separated solid was filtered off and crystallized from *n*-butanol (Table I).

Synthesis of Compound 6

A mixture of 4 g anhydrous potassium carbonate, compound **1** (0.004 mol) in DMF (20 ml), and catalytic amount of TBAB was treated with 0.004 mol of CS_2 and stirred for 4 h at 60°C. After that, chloroacetonitrile (0.004 mol) was added, and the mixture was stirred for additional 16 h at 70°C. The reaction mixture was filtered, and the filtrate was added to ice-cold water. The separated solid was filtered off and crystallized from DMF/H_2O to give compound **6** (Table I).

Synthesis of Compound 7

To a solution of compound **1** (0.01 mol) in dry pyridine (30 ml), was added phosphorus pentasulphide (0.01 mol). The reaction mixture was refluxed for 7 h, filtered while hot, and concentrated. The precipitate was filtered off and crystallized from pyridine/H_2O (Table I).

Synthesis of Compound 8

A mixture of compound **7** (0.01 mol), and malononitrile (0.01 mol) in DMF (20 ml) was refluxed. The evalution of H_2S was ceased ($\simeq$20 h). The reaction mixture was cooled to room temperature and poured into ice-cold water (100 ml). The separated solid was filtered off and crystallized from DMF/H_2O (Table I).

Synthesis of Compounds 9a,b

General Procedure

A mixture of compound **8** (0.004 mol), benzaldehyde or *p*-nitrobenzaldehyde (0.004 mol), and a catalytic amount of anhydrous sodium acetate in DMF (20 ml) was refluxed for 7 h. The reaction mixture was poured into ice-cold water (100 ml). The solid product was filtered off and crystallized from the suitable solvent (Table I).

Synthesis of Compound 10

A mixture of 4 g anhydrous potassium carbonate, compound **8** (0.006 mol), and catalytic amount of TBAB in DMF (20 ml) was treated with 0.006 mol of CS_2 and stirred for 4 h at room temperature. Methyl iodide (0.012 mol) was added, and the mixture was stirred for an additional 4 h at room temperature. The reaction mixture was filtered off, and the filtered was added into ice-cold water. The product was filtered off and crystallized from DMF/H_2O (Table I).

Synthesis of Compound 11

A mixture of compound **10** (0.002 mol) and aniline (0.002 mol) in DMF (15 ml) was refluxed for 3 h. The reaction mixture was poured into ice-cold water (100 ml) containing a few drops of dil. HCl. The separated solid was filtered off, washed with water, dried, and crystallized from DMF/H_2O (Table I).

Synthesis of Compounds 12–15a,b

General Procedure

To a solution of compound **8** (0.002 mol) in DMF (20 ml) was added in portions the amine or phenol (0.006 mol) in DMF (20 ml). The mixture was refluxed for 2 h. The reaction mixture was added into ice-cold water (100 ml). The precipitate was filtered off, dried, and crystallized from the proper solvent (Table I).

REFERENCES

[1] M. C. Hosur, M. B. Talawar, U. V. Laddi, R. S. Bennur, and S. C. Bennur, *Indian J. Chem.*, **34B,** 707 (1995).

[2] R. P. Srivastava, V. V. Kumar, S. Bhatia, and S. Sharma, *Indian J. Chem.*, **34B,** 209 (1995).

[3] S. Sudan, R. Gupta, R. Swara, G. B. Singh, S. Bani, and P. L. Kachroo, *Indian J. Chem*., **34B,** 458 (1995).
[4] M. H. Khan and S. Giri, *Indian J. Chem*., **34B,** 1007 (1995).
[5] J. Mohan and G. S. R. Anjaneyulug, *Curr. Sci*., **58,** 1028 (1989).
[6] A. M. M. E. Omar and O. M. Aboulwafa, *J. Heterocyclic. Chem*., **23,** 1339 (1986).
[7] A. R. Rasad, T. Ramalingamat, A. B. Rao, P. W. Diwan, and P. B. Sattur, *Indian J. Chem*., **25B,** 556 (1986).
[8] A. A. Deshmukh, M. K. Mody, T. Ramalingamt, and P. B. Sattur, *Indian J. Chem*., **25B,** 793 (1985).
[9] F. P. Invidiata, S. Grimaudo, P. Giammanco, and L. Giammanco, *Farmaco*., **46,** 1489 (1991).
[10] M. Kidwai, P. Sapra, P. Misra, R. K. Saxena, and M. Singh, *Bioorganic and Medicinal Chemistry*, **9**(2), 217 (2001).
[11] K. M. Hussain and G. Somari, *Indian J. Chem. Sect. B*, **34**(11), 1007 (1995).
[12] M. T. M. El-Wassimy, M. Abdel-Rahman, A. B. A. G. Ghattas, and O. A. A. Abd Allah, *Phosphorus, Sulfur, and Silicon*, **70,** 99 (1992).
[13] A. B. A. G. Ghattas, H. M. Moustafa, O. A. Abd Allah, and A. A. Amer, *Synthetic Comm.*, **31**(16), 2447 (2001).
[14] A. B. A. G. Ghattas, O. A. Abd Allah, H. M. Moustafa, and A. A. Amer, *Egypt. J. Chem*., 2002 (under pub.).
[15] S. A. M. Metwally, G. M. El-Naggar, M. I. Younis, T. I. El-Emary, and M. H. Elnagdi, *Liebigs Ann. Chem*., 1037 (1989).