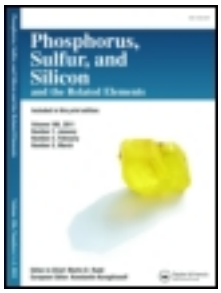


Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Synthesis of Polyfused Thieno(2,3- b)thiophenes Part 3: Synthesis of Thienopyrimidinotetrazole, Thienopyrimidinotriazepine, Thienopyrimidinotriazine, Thienopyrimidinotriazole and Pyrazolylthienopyrimidine Derivatives

A. Khodairy [a]

[a] Chemistry Department, Faculty of Science, South Valley University, Sohag, Egypt

Available online: 27 Oct 2010

To cite this article: A. Khodairy (2003): Synthesis of Polyfused Thieno(2,3- b)thiophenes Part 3: Synthesis of Thienopyrimidinotetrazole, Thienopyrimidinotriazepine, Thienopyrimidinotriazine, Thienopyrimidinotriazole and Pyrazolylthienopyrimidine Derivatives, Phosphorus, Sulfur, and Silicon and the Related Elements, 178:4, 893-901

To link to this article: http://dx.doi.org/10.1080/10426500307790

Phosphorus, Sulfur and Silicon, 2003, Vol. 178:893–901

1042-6507/03 $12.00 + .00
DOI: 10.1080/10426500390198066

SYNTHESIS OF POLYFUSED THIENO(2,3-*b*)THIOPHENES PART 3: SYNTHESIS OF THIENOPYRIMIDINOTETRAZOLE, THIENOPYRIMIDINOTRIAZEPINE, THIENOPYRIMIDINOTRIAZINE, THIENOPYRIMIDINOTRIAZOLE AND PYRAZOLYLTHIENOPYRIMIDINE DERIVATIVES

A. Khodairy
Chemistry Department, Faculty of Science, South Valley University, Sohag, Egypt

(Accepted October 2, 2002)

*2,9-Dihydrazinobipyrimidino(2,3-*b*)thienothiophene (**2**) was reacted with nitrous acid, ethoxymethylenemalononitrile, bromomalononitrile, triethyl formate, CS_2 or isatine to afford the corresponding tetrazole, triazepine, triazine, and triazole derivatives **3–8** respectively. Treatment of compound **2** with cyclohexylidenenitriles, acetylacetone, ethyl acetoacetate, 2-hydroxyacetophenone, or S,S-acetals afforded the corresponding pyrazole derivatives **9–15** respectively.*

Keywords: Pyrazol-2-ylpyrimidinothienothiophene; tetrazolopyrimidinothienothiophene; thienopyrimidine; triazepinopyrimidinothienothiophene; triazinopyrimidinothienothiophene derivatives

Thieno(2,3-b)thiophenes have been studied[1] and developed for different purposes in the pharmaceutical field and have been tested as, depending on the nature of the substituents, potential antiviral,[2] antibiotic,[3] antiglaucoma,[4] analgesic, and antipyretic[5] drugs.

In our previous work,[6–8] we reported the synthesis of thieno(3,2-d)pyrimidine, thieno(3,2-d)thiazine, thienopyrrolopiprazine, and thienothiazaphospholine; here we undertook the synthesis of some new heterocyclic compounds containing thieno(3,2-d)pyrimidine moiety fused

See Refs. 6 and 7 for Parts 1 and 2.

Address correspondence to A. Khodairy, Chemistry Department, Faculty of Science, Sohag 82524, Egypt. E-mail: Khodairy@yahoo.com

TABLE I Analytical and Spectral Data of the New Compounds

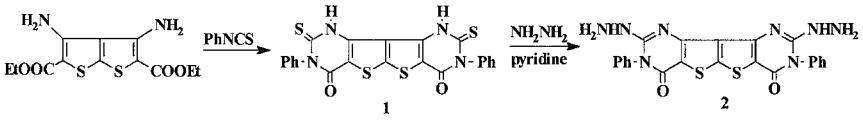
Product No.	m.p. (°C)[a]	Yield (%) Cryst. solvent	Mol. form. (mol. wt.)	Analytical data[b] cal./found				IR (Cm^{-1})[c]	^{1}H-NMR ∂ (ppm)[d]
				C	H	N	S		
2	170–172	66 Dioxane	$C_{22}H_{16}N_8O_2S_2$ (488.55)	54.09 54.30	3.30 3.51	22.93 22.75	13.12 13.35	3340, 3221, 3112 (NH, NH_2), 1690 (CO), 1621 (C═N)	8.0–7.2 (m, 10H, arom.), 6.4 (s, 2H, 2 NH), 5.5–5.2 (br, 4H, $2NH_2$)
3	140–142	90 Dioxane	$C_{22}H_{10}N_{10}O_2S_2$ (510.52)	51.75 51.50	1.97 1.61	27.43 27.20	12.56 12.24	1688 (CO), 1621 (C═N)	8.0–7.2 (m, 10H, arom.)
4	211	29 Ethanol	$C_{30}H_{16}N_{12}O_2S_2$ (640.67)	56.24 56.61	2.51 2.78	26.23 26.55	10.00 10.24	3328, 3211 (NH_2), 2212 (CN), 1689 (CO)	9.1 (s, 2H, 2 ═CH), 8.0–7.2 (m, 10H, arom.), 5.6 (br, 4H, $2NH_2$)
5	185–187	40 *n*-butanol	$C_{28}H_{16}N_{12}O_2S_2$ (616.65)	54.53 54.31	2.61 2.72	27.25 27.56	10.39 10.64	3249, 3119 (NH_2), 2210 (CN), 1698 (CO)	10.0 (s, 2H, 2NH), 8.0–7.2 (m, 10H, arom.), 5.6 (br, 4H, $2NH_2$)
6	320	60 Dioxane	$C_{24}H_{12}N_8O_2S_2$ (508.54)	56.98 56.60	2.37 2.60	22.03 22.37	12.61 12.85	1690 (CO), 1621 (C═N)	7.7–6.9 (s, 2H, 2 ═CH_2), 8.3–7.0 (m, 10H, arom.)
7	299	69 *n*-butanol	$C_{24}H_{12}N_8O_2S_4$ (572.67)	50.33 50.59	2.11 2.33	19.56 19.79	22.39 22.51	3340 (NH), 1688 (CO), 1455 (CS)	10.0 (s, 2H, 2NH), 8.0–7.2 (m, 10H, arom.)
8	210–212	80 DMF	$C_{38}H_{18}N_{10}O_2S_2$ (710.76)	38.05 38.30	2.55 2.70	19.70 19.90	9.02 9.25	1690 (CO), 1600 (C═N)	8.0–7.2 (m, 18H, arom.) 8.0–7.2 (m, 18H, arom.)
9	322	90 Dioxane	$C_{40}H_{36}N_{12}O_2S_2$ (780.94)	61.52 61.20	4.64 4.40	21.52 21.69	8.21 8.34	3345, 3328, 3211 (NH+ NH_2), 2212 (CN), 1689 (CO)	9.0 (s, 2H, 2NH), 8.0–7.2 (m, 10H, arom.), 5.5–5.3 (br, 4H, $2NH_2$), 3.0–1.5 (m, 10H, $5CH_2$)
10	216	70 Acetone	$C_{40}H_{35}N_{10}O_4S_2$ (783.92)	61.28 61.41	4.50 4.61	17.86 17.57	8.18 8.37	3554 (OH), 3320 (NH), 2110 (CN), 1678 (CO)	9.0 (s, 2H, 2NH), 8.0–7.2 (m, 10H, arom.), 3.5 (br, 2H, 2OH), 3.0–1.5 (m, 10H, $5CH_2$)

11	261	93 Methanol	$C_{32}H_{24}N_8O_2S_2$ (616.73)	62.32 62.59	3.92 3.60	18.17 18.34	10.39 10.54	2988 ($CH_{aliph.}$), 1689 (CO)	7.4–6.6 (m, 10H, aromatic), 6.0 (s, 2H, 2 ═CH), 2.5 (br, 12H, $4CH_3$)
12	188	30 Dioxane	$C_{3o}H_{20}N_8O_4S_2$ (620.67)	58.43 58.71	3.24 3.54	18.05 18.28	10.33 10.56	33321 (NH), 1699, 1700 (CO)	10.0 (s, 2H, 2NH), 7.4–6.6 (m, 10H, aromatic), 6.2 (s, 2H, 2 ═CH), 2.5 (s, 6H, $2CH_3$)
13	197–199	75 DMF	$C_{38}H_{24}N_8O_2S_2$ (688.79)	66.26 66.51	3.51 3.71	16.26 16.48	9.31 9.53	1690 (CO), 1600 (C═N)	7.3–6.7 (m, 10H, aromatic), 2.4 (s, 6H, $2CH_3$)
14a	165–167	90 Ethanol	$C_{30}H_{16}N_{12}O_2S_4$ (704.79)	51.13 51.49	2.29 2.55	23.84 23.57	18.20 18.47	3328, 3211 (NH_2), 2776 (SH), 2190 (CN), 1680 (CO)	8.0–7.4 (m, 10H, aromatic), 5.3–5.0 (br, 4H, $2NH_2$), 2.3 (s, 2H, 2SH)
14b	109–111	95 Ethanol	$C_{34}H_{26}N_{10}O_6S_4$ (798.91)	51.12 51.30	3.28 3.49	17.53 17.30	16.05 16.22	3328, 3211 (NH_2), 2776 (SH), 1744 (CO), 1679 (CO)	8.0–7.4 (m, 10H, aromatic), 5.5–5.2 (br, 4H, $2NH_2$), 4.4–4.1 (q, 4H, $2CH_2$), 2.3 (s, 2H, 2SH), 1.4–1.1 (t, 6H, $2CH_3$)
15a	154	35 Dioxane	$C_{32}H_{20}N_{12}O_2S_4$ (732.52)	52.47 52.68	2.75 2.51	22.95 22.62	17.51 17.78	3250, 3111 (NH_2), 2210 (CN), 1695 (CO)	8.0–7.4 (m, 10H, aromatic), 5.3–5.0 (br, 4H, $2NH_2$), 2.3 (s, 6H, $2SCH_3$)
15b	243–245	58 DMF	$C_{36}H_{30}N_{10}O_6S_4$ (826.96)	52.29 52.40	3.65 3.38	16.94 16.79	15.51 51.70	3328, 3211 (NH_2), 1737 (CO), 1690 (CO)	8.0–7.4 (m, 10H, aromatic), 5.5–5.2 (br, 4H, $2NH_2$), 4.4–4.1 (q, 4H, $2CH_2$), 2.3 (s, 6H, $2SCH_3$), 1.4–1.1 (t, 6H, $2CH_3$)

[a]Uncorrected.
[b]Satisfactory microanalysis obtained C; ±0.35, H; ±0.4, N; ±0.3, S; ±0. 3.
[c]Measured by Nicolet FT-IR 710 Spectrophotometer.
[d]Measured by a Varian EM 360 L spectrometer at 60 MHZ using TMS as internal standard and DMSO as a solvent.

with tetrazol, triazepine, triazine, triazole, and attached to a pyrazole nucleus.

2,9-Dihydrazino-3,8-diphenyl-4,7-dioxo-bipyrimidino(5′,6′-b)thieno (2,3-b)thiophene **2** was synthesized in 90% yield from the reaction of bisthieno(3,2-d)pyrimidine-2-thione derivative **1**[6] with hydrazine hydrate in pyridine. IR spectrum showed an absorption bands at 3400, 3340, 3100 Cm^{-1} (NH,NH_2) and 1689 Cm^{-1} (CO). ^{1}H-NMR (δ, ppm) showed signals at 8.0–7.2 (m, 10H, aromatic), 6.4 (s, 2H, 2NH) and 5.5–5.2 (br, 4H, $2NH_2$) respectively (cf. Table I).



1 2

Compound **2** was investigated as starting material for the synthesis of many heterocyclic compounds fused to thieno(3,2-d)pyrimidine moiety. Thus, compound **2** was treated with nitrous acid[9] to afford tetrazolopyrimidino(2,3-b)thienothiophene derivative **3** (cf. Scheme 1, Table I).

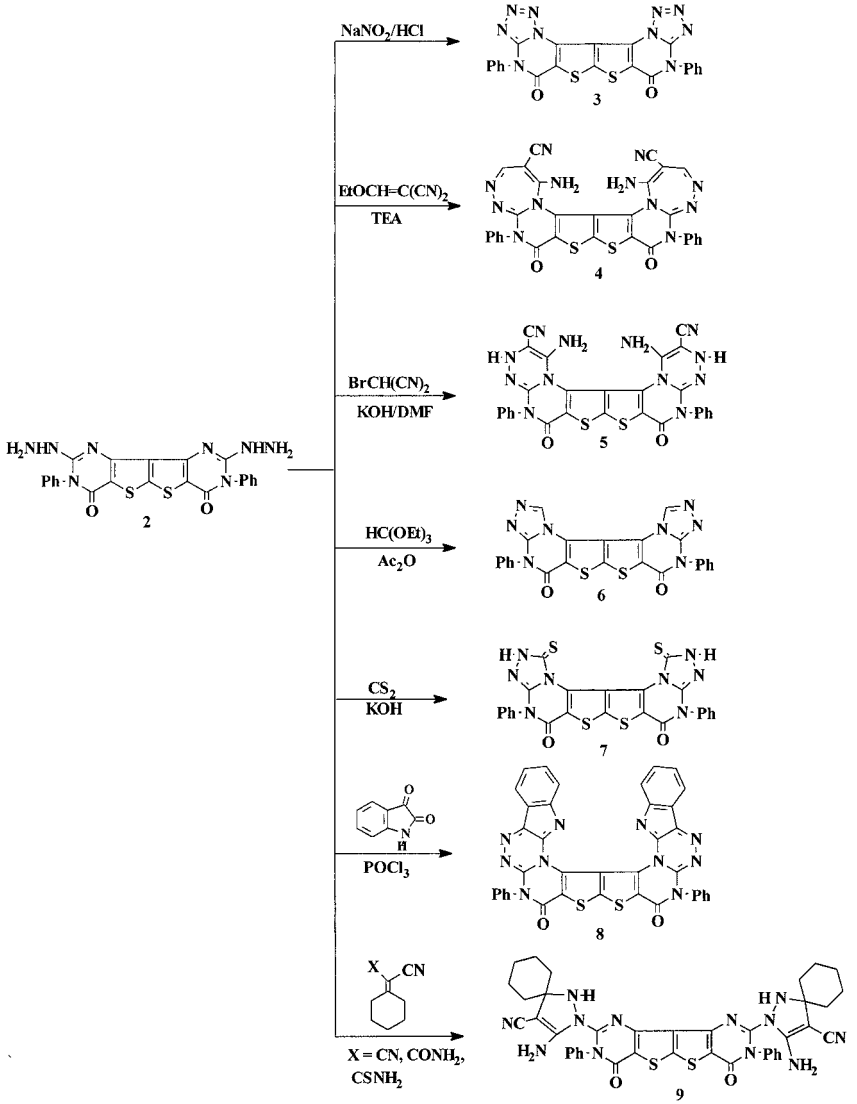
Treatment of compound **2** with ethoxymethylenemalononitrile in the presence of triethylamine, afforded the corresponding triazepinopyrimidino(2,3-b)thienothiophene derivative **4** (cf. Scheme 1, Table I).

Cyclization of compound **2** with bromomalononitrile gave the corresponding triazinopyrimidino(2,3-b)thienothiophene derivative **5**. IR spectrum showed an absorption bands at 3400, 3340, 3100 Cm^{-1} (NH,NH_2) and 2100 Cm^{-1} (CN) (cf. Scheme 1, Table I).

The reaction of compound **2** with triethylorthoformate[10] in the presence of triethylamine or carbon disulphide[9] in the presence of potassium hydroxide gave the corresponding triazolopyrimidino(2,3-b)thienothiophene derivatives **6** and **7** respectively (cf. Scheme 1, Table I).

Treatment of compound **2** with isatine in the presence of $POCl_3$ afforded the corresponding indolotriazinopyrimidino(2,3-b)thienothiophene derivative **8** (cf. Scheme 1, Table I).

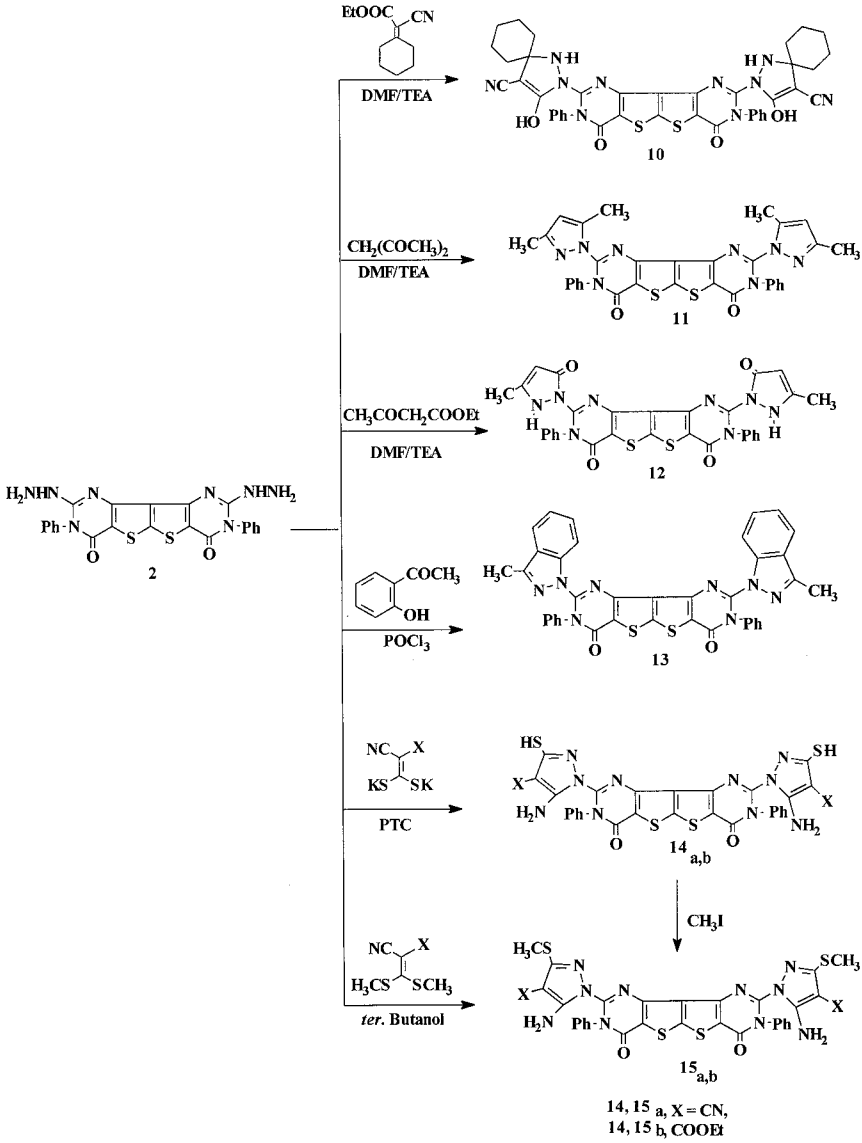
Compound **2** was allowed to react with cyclohexylidenemalononitrile, cyclohexylidenecyanoacetamide, cyclohexylidenecyanothioacetamide, or ethyl cyclohexylidenecyanoacetate in refluxing DMF and triethylamine to give 2-pyrazolylpyrimidino(2,3-b)thienothiophene derivatives **9** and **10** respectively. The reaction pathway[11] was assumed to proceed via a nucleophilic addition of the NH_2 group to the ethylenic bond, followed by a nucleophilic attack of the NH group to the CN, CO(amide), CS, or CO(ester) groups with elimination of



SCHEME 1

H_2O, H_2S, or EtOH molecules, respectively (cf. Schemes 1 and 2, Table I).

Condensation of compound **2** with acetylacetone or ethyl acetoacetate in the presence of triethylamine afforded the corresponding (3,5-dimethylpyrazol-2-yl)- and (3-methyl-5-oxopyrazolin-2-yl)pyrimidino-(2,3-b)thienothiophene **11** and **12** respectively (cf. Scheme 2, Table I).



SCHEME 2

Treatment of compound **2** with 2-hydroxyacetophenone and $POCl_3$ gave the corresponding 2-pyrazolylpyrimidinothienothiophene **13** (cf. Scheme 2, Table I).

Finally, compound **2** was reacted with CS_2 and malononitrile or ethyl cyanoacetate in 1:1:1 molar ratio under PTC conditions

[K_2CO_3/DMF/tetrabutylammonium bromide (TBAB)] to give the corresponding (3-mercapto-4-cyano(carbethoxy)-5-aminopyrazol-2-yl)thieno(3,2-d)pyrimidine derivative **14a**,**b**. The reaction pathway[12] was assumed to proceed via the addition of the NH_2 group to the ethylenic bond with elimination of H_2S molecule, followed by a nucleophilic attack of the NH group to the CN group or to the carbethoxy group with elimination of ethanol molecule. Compounds **14a**,**b** were alkylated with methyl iodide in the presence of sodium hydroxide to afford S-Me derivatives **15a**,**b**. Another route for the synthesis of compounds **15a**,**b** is the reaction of compound **2** with cyanoketene S,S acetals in refluxing ter butanol for 48 h (cf. Scheme 2, Table I).

EXPERIMENTAL

Synthesis of Compound 2

To a suspension of compound **1** (0.01 mmol) in pyridine (10 ml) hydrazine hydrate (0.02 mmol) was added. The reaction mixture was refluxed for 10 h. After cooling, it was poured into a mixture of ice-water (200 ml) and HCl (10 ml). The separated solid was collected by filtration, washed with water, dried, and crystallized from dioxane (Table I).

Synthesis of Compound 3

A solution of compound **2** (0.01 mmol) in conc. HCl (4 ml) and water (3 ml) was cooled in an ice bath at 0–5°C, whereupon a cold solution of sodium nitrite (0.06 mmol) in water (5 ml) was added dropwise while stirring. The reaction mixture was set aside for 3 h. The separated solid was filtered, washed with water, dried, and crystallized from dioxane (cf. Scheme 1, Table I).

Synthesis of Compounds 4, 9–12 (General Procedure)

Compound **2** (0.003 mmol) was added to a stirred solution of the appropriate reagent (0.006 mmol) namely, ethoxymethylenemalononitrile, cyclohexylidenemalononitrile, cyclohexylidenecyanoacetamide, cyclohexylidenecyanothioacetamide, ethyl cyclohexylidenecyanoacetate, acetyacetone, and ethyl acetoacetate in presence of triethylamine (0.006 mmol) in DMF (50 ml). The reaction mixture was refluxed for 3 h, after cooling it was poured into a mixture of ice-water (200 ml) and HCl (10 ml). The separated solid was collected by filtration, washed with water, dried, and crystallized from appropriate solvent (cf. Schemes 1 and 2, Table I).

Synthesis of Compounds 5 and 7 (General Procedure)

A mixture of compound **2** (0.02 mmol), potassium hydroxide (0.04 mmol) and bromomalononitrile (0.04 mmol) or carbon disulphide (0.04 mmol) in DMF (20 ml) was refluxed for 4 h. On cooling, the precipitated solid was filtered, dried, washed with ether, dissolved in water, and the product was reprecipitated by addition of HCl (20 ml). The product was filtered, washed with water, dried, and crystallized from n-butanol (cf. Scheme 1, Table I).

Synthesis of Compound 6

To a stirred solution of compound **2** (0.01 mmol) in acetic anhydride (20 ml), triethylorthoformate (0.02 mmol) was added. The reaction mixture was refluxed for 12 h, evaporated in vacuo and the remaining product was triturated with water and the residual solid was collected by filtration and crystallized from dioxane (cf. Scheme 1, Table I).

Synthesis of Compounds 8 and 13 (General Procedure)

To a stirred solution of compound **2** (0.01 mmol) in $POCl_3$ (30 ml), isatine (0.02 mmol), or 2-hydroxyacetophenone (0.02 mmol) was added. The reaction mixture was refluxed for 2 h, evaporated in vacuo and the remaining product was triturated with pet. ether (60–80°C) and the residual solid was collected by filtration and crystallized from DMF (cf. Schemes 1 and 2, Table I).

Synthesis of Compounds 14a,b (General Procedure)

A mixture of a proper active methylene compound (0.04 mmol), CS_2 (0.045 mmol), anhydrous potassium carbonate (3 gm), a catalytic amount of TBAB, and dioxane (20 ml) was stirred for 40 min at 60°C. To the dianionic ambident was added compound **2** (0.02 mmol). The reaction mixture was stirred for 6 h at 40°C, filtered, and evaporated in vacuo. The residual solid was washed with water, collected by filtration, and crystallized from ethanol (cf. Schemes 1 and 2, Table I).

Synthesis of Compounds 15a,b

Method A

To a stirred solution of compounds **14a**,**b** (0.01 mmol) in DMF (30 ml), methyl iodide (0.02 mmol) and potassium hydroxide (0.02 gm) were added. The reaction mixture was refluxed for 2 h, evaporated in vacuo

and the remaining product was triturated with water and the residual solid was collected by filtration and crystallized from the suitable solvent (cf. Scheme 2, Table I).

Method B

An equimolar amount (0.02 mmol) of compound **2** and the proper S,S-acetals (0.04 mmol) were dissolved in ter. butanol (30 ml). The reaction mixture was refluxed until the evolution of MeSH ceased (48 h), evaporated in vacuo and the remaining product was triturated with pet. ether (40–60°C) and the residual solid was collected by filtration and crystallized from dioxane (cf. Scheme 2, Table I).

REFERENCES

[1] A. Comel and G. Kirsch, *J. Heterocyclic. Chem*., **38,** 1167 (2001).
[2] D. Peters, A. B. Hornfeldt, and S. Gronowitz, *J. Heterocyclic. Chem*., **27,** 2165 (1990).
[3] S. Kukolija, S. E. Draheim, B. J. Graves, D. C. Hunden, J. L. Pfeil, R. D. G. Cooper, J. L. Ott, and F. T. Couter, *J. Med. Chem*., **28,** 1896 (1995).
[4] J. D. Prugh, G. D. Hartman, P. J. Mallorga, B. M. McKeever, S. R. Michelson, M. A. Murcko, H. Schwam, R. L. Smith, J. M. Sondey, J. P. Springer, and M. F. Surgrue, *J. Med. Chem*., **24,** 1805 (1991).
[5] J. L. Fabre, D. Fage, and C. James, *Ger. Pat.*, 2,703,624 (1976); *C.A*., **87,** 168000v.
[6] A. Khodairy and H. Abdel-Ghany, *Phosphorous, Sulfur, and Silicon*, **162,** 259 (2000).
[7] H. Abdel-Ghany and A. Khodairy, *Phosphorous, Sulfur, and Silicon*, **166,** 45 (2000).
[8] A. M. M. Soliman, A. Khodairy, and E. A. Ahmed, *Phosphorous, Sulfur, and Silicon*, **178,** 649 (2003).
[9] A. M. Kamel El-Dean, *Monatshefte fur Chemie*, **129,** 523 (1998).
[10] M. Abass, *Synthetic Communication*, **30,** 2735 (2000).
[11] A. Khodairy, *Synthetic Communication*, **31,** 2697 (2001).