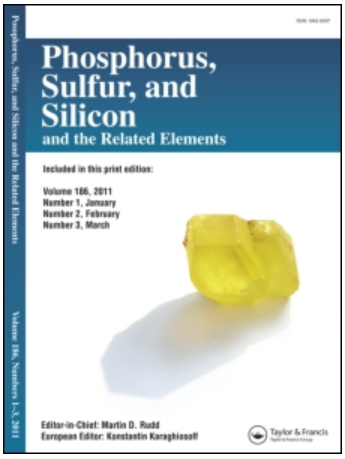


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS OF THIENO(2, 3-D)-1, 3-THIAZINES AND RELATED STRUCTURES

A. M. Soliman[a]
[a] Chemistry Department, Faculty of Science, Sohag, Egypt

To cite this Article Soliman, A. M.(1994) 'SYNTHESIS OF THIENO(2, 3-D)-1, 3-THIAZINES AND RELATED STRUCTURES', Phosphorus, Sulfur, and Silicon and the Related Elements, 97: 1, 1 — 8
To link to this Article: DOI: 10.1080/10426509408020721
URL: http://dx.doi.org/10.1080/10426509408020721

Phosphorus, Sulfur, and Silicon, 1994, Vol. 97, pp. 1–8
Reprints available directly from the publisher
Photocopying permitted by license only

SYNTHESIS OF THIENO(2,3-d)-1,3-THIAZINES AND RELATED STRUCTURES

A. M. SOLIMAN
Chemistry Department, Faculty of Science, Sohag, Egypt

(Received February 16, 1994; in final form September 23, 1994)

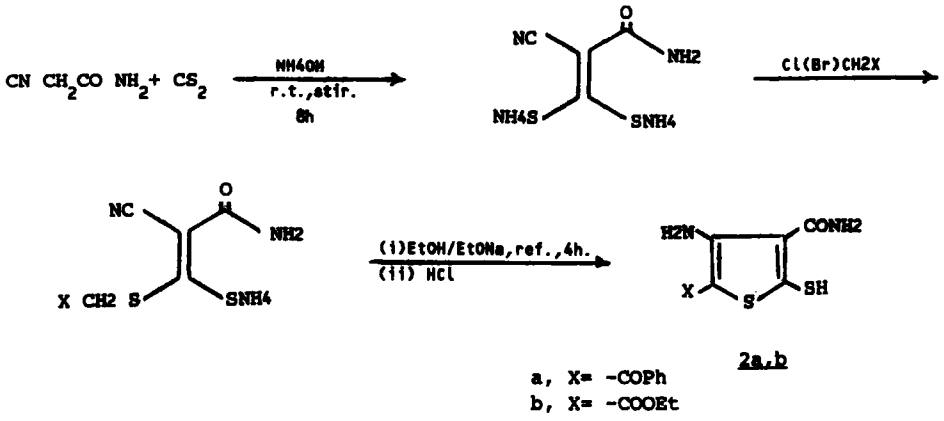
4-Amino-3-carbonyl-2-mercapto-5-(substituted)thiophene 2a,b was reacted with ethylchloroformate, benzoylchloride, benzaldehyde or acetic anhydride to give the corresponding thienothiazine 4a,b; 5a,b; 6a,b or thienooxazine 7. The N-pyrryl derivative of 2b or 4b was cyclized into the corresponding pyrolothienothiazine derivatives 10 or 14, respectively.

Key words: Thienothiazine, thienooxazine, pyrrolothienothiazine, 2,5-dimethoxytetrahydrofuran.

INTRODUCTION

Ketene S,S-actals prepared by the reaction of ketones[1] or nitriles[2] as well as heterocyclic ketene N,N-[3–9] or N-S-acetals[5,10–14] have become a subject of current interest. Although several papers have appeared regarding their preparation and structural studies in recent literature[15] the synthetic utility of these intermediates has not been extensively explored.[16] In our earlier studies[17–19] we have reported the use of cyanoketene S,S-acetals or heterocyclic ketene N,O-acetals in the synthesis of various heterocycles.

The objective of the present investigation is to obtain a suitably substituted thiophene ring system with a view to synthesizing thieno(2,3-d)-1,3-thiazines and related structures. Keten S,S-acetal prepared by the reaction of cyanoactamide with CS_2 in ammonia solution at room temperature offers a convenient dithioic acid derivative. This product was alkylated with α-bromoactophenone or ethylchloroacetate in boiling EtOH/EtONa solution followed by acidification. The main substrate 4-amino-3-carbamoyl-2-mercapto-5-(substituted)thiophene 2 was obtained in high yield.

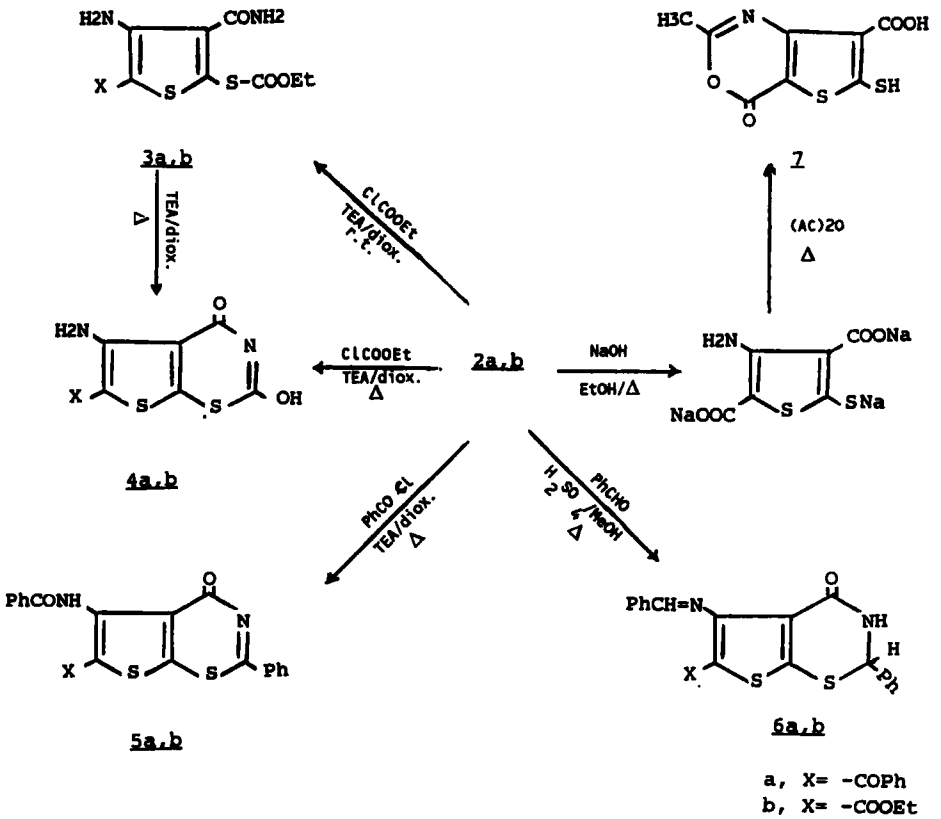


2a,b

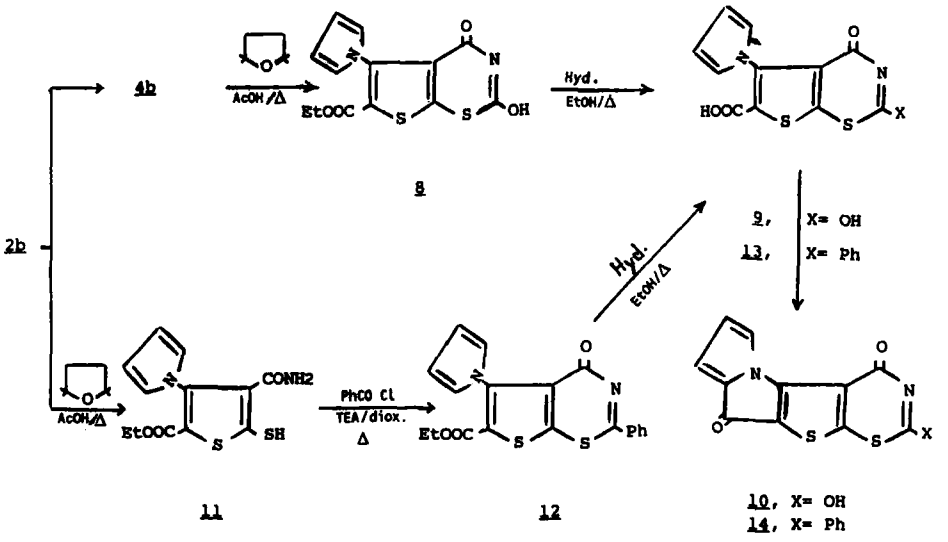
a, X= -COPh
b, X= -COOEt

The reaction of compound 2a,b with ethylchloroformate or benzoylchloride in refluxing dioxane/triethylamine(TEA) afforded the corresponding thieno(2,3-d)-1,3-thiazine derivatives 4a,b and 5a,b, respectively. The reaction mechanism involves dehydrohalogenation followed by ring closure. The precursor of compound 4a,b was obtained when the reaction was carried out at room temperature. Compound 2a,b was reacted with benzaldehyde in methanol in the presence of 20% H_2SO_4 yielding 2,3-dihydrothieno(2,3-d)-1,3-thiazin-4-one derivative 6a,b. This is formed *via* a nucleophilic attack of the mercapto group at the carbonyl function followed by dehydration and ring closure. The carbethoxy and carbamoyl groups in compound 2b were hydrolyzed in a 12% NaOH solution. The corresponding dicarboxylic acid salt was precipitated in the reaction media, filtered off, and cyclized in boiling acetic anhydride into 7-carboxy-5-mercapto-2-methyl-thieno(3,2-d)-1,3-oxazin-4-one 7.

In connection with our work on the synthesis of heterocyclic systems containing a bridgehead nitrogen atom[20–22] and in light of several reports[23–25] which indicate that aryl or heteroaryl pyrroles are useful substrates for intramolecular cyclization reactions, compound 4b was used as a starting material. It was reacted with 2,5-dimethoxytetrahydrofuran in boiling acetic acid and the corresponding 6-carbethoxy-2-hydroxy-5-(1-pyrryl)-thieno-(2,3-d)-1,3-thiazin-4-one 8 was obtained.



SCHEME I



SCHEME II

TABLE I

Physical and analytical data of the prepared compounds

compound NO.	M.P °C (cryst.solv.)	Yield %	Mol.Formula (M. Wt)	Analytical data Calc./ Found (%) C	H	N	S
2a	207	85	$C_{12}H_{10}N_2O_2S_2$	51.65	3.87	10.04	22.98
	(EtOH)		(279.05)	51.35	3.75	9.9	22.85
2b	248	78	$C_8H_{10}N_2O_3S_2$	38.90	4.37	11.43	25.96
	(EtOH)		(247.01)	38.65	4.25	11.40	26.10
3a	190	76	$C_{15}H_{14}N_2O_4S_2$	51.27	4.30	7.97	18.25
	(Benzene)		(351.40)	51.45	4.12	7.81	18.08
3b	182	73	$C_{11}H_{14}N_2O_5S_2$	41.37	4.73	8.77	20.08
	($CHCl_3$)		(319.36)	41.49	4.56	8.62	20.25
4a	255	68	$C_{13}H_8N_2O_3S_2$	51.21	2.83	9.19	21.03
	(EtOH)		(304.90)	51.01	2.71	9.34	21.22
4b	267	70	$C_9H_8N_2O_4S_2$	39.61	3.17	10.27	23.50
	(Dioxane)		(272.86)	39.76	3.01	10.40	23.31
5a	220	67	$C_{26}H_{16}N_2O_3S_2$	66.48	3.68	5.96	13.65
	($CHCl_3$)		(469.67)	66.71	3.55	5.79	13.81
5b	232	58	$C_{12}H_{16}N_2O_4S_2$	60.37	3.95	6.40	14.65
	(EtOH)		(437.63)	60.29	3.79	6.56	14.79

TABLE I (*Continued*)

compound NO.	M.P °C (cryst.solv.)	Yield %	Mol.Formula (M. Wt)	Analytical data Calc./ Found (%) C	H	N	S
6a	240	69	$C_{26}H_{18}N_2O_2S_2$	68.50	4.26	6.15	14.07
	(MeOH)		(455.83)	68.66	4.14	6.01	14.23
6b	258	73	$C_{22}H_{18}N_2O_3S_2$	62.35	4.59	6.61	15.13
	(Dioxane)		(423.79)	62.52	4.42	6.75	15.01
7	220	55	$C_8H_5N\ O_4S_2$	39.44	2.22	5.75	26.32
	(EtOH)		(243.60)	39.61	2.38	5.58	26.47
8	195	75	$C_{13}H_{10}N_2O_4S_2$	48.33	3.34	8.67	19.85
	(Benzene)		(323.06)	48.14	3.21	8.81	19.99
9	205	72	$C_{11}H_6N_2O_4S_2$	44.83	2.20	9.51	21.76
	(EtOH)		(294.72)	44.98	2.03	9.37	21.91
10	223	56	$C_{11}H_{14}N_2O_3S_2$	47.77	1.56	10.13	23.18
	(DMF)		(276.56)	47.65	1.69	9.97	23.34
11	280	82	$C_{12}H_{12}N_2O_3S_2$	48.49	4.36	9.47	21.57
	(Dioxane)		(297.21)	48.63	4.21	9.61	21.42
12	240	55	$C_{19}H_{14}N_2O_3S_2$	59.51	3.94	7.31	16.72
	(THF)		(383.44)	59.38	4.09	7.19	16.86
13	270	76	$C_{17}H_{10}N_2O_3S_2$	57.50	3.04	7.89	18.06
	($CHCl_3$)		(355.10)	57.63	3.19	7.73	18.21
14	285	52	$C_{17}H_8N_2O_2S_2$	60.60	2.56	8.41	19.03
	(DMF)		(336.94)	60.47	2.69	8.55	18.89

Hydrolysis of compound 8 in ethanolic sodium hydroxide solution afforded the corresponding acid 9. This was cyclized in boiling polyphosphoric acid to the tetraheterocyclic system, 2-hydroxy-pyrrolo(2,1-e)pyrrolo(3,2-b)thieno(2,3-d)-1,3-thiazin-4,8-dione 10. Compound 2b was converted into its N-pyrryl derivative 11 under the same reaction conditions followed by reaction with benzoyl chloride. The product 6-carbethoxy-2-phenyl-5-(1-pyrryl)thieno(2,3-d)-1,3-thiazin-4-one 12 was hydrolized to the corresponding acid 13. It was then cyclized in boiling PPA to 2-phenyl-pyrrolo(2,1-e)pyrrolo(3,2-b)thieno(2,3-d)-1,3-thiazin-4,8-dione 14.

EXPERIMENTAL

All melting points were determined on a Kofler melting point apparatus and were uncorrected. IR spectra were obtained on a Pye-Unicam SP3-100 infrared spectrophotometer. ^{1}H-NMR spectra were obtained on a Varian EM 360 A at 60 MHz using TMS as the internal standard. Elemental analyses were carried out on an elemental analyzer 240C.

TABLE II

IR and ^{1}H-NMR spectra of the prepared compounds

comp.	IR(KBr) Cm^{-1}	^{1}H-nmr (DMSO-d_6) ,(δppm)
2a	3420,3330,3298,3130,($2NH_2$) 1690,1660(2C=O)	7.80-7.50(m,5H,arm.), 7.60-7.00(m, ,4H,$2NH_2$), 3.60 (br,1H,SH).
2b	3450,3360,3290,3100,($2NH_2$), 2978-2950(C-H)alif.,1702- ,1660(2C=O)	7.80-7.50(br,4H,$2NH_2$),4.50-4.10 (q,2H,CH_2,ester),1.5-1.2(tr,3H, CH_3).
3a	3447,3382,3330,3188($2NH_2$), 2990-2955(C-H)alif.,1723, ,1685(2C=O)	7.90-7.30(m,5H,arom.),6.90-6.40 (br,4H,$2NH_2$),4.60-4.10(q,2H,CH_2, ester),1.50-1.10(tr,3H,CH_3).
3b	3455,3355,3250,3150($2NH_2$), 2995-2945(C-H)alif.,1725, 1660(2C=O)	7.00-6.50(br,$2NH_2$),4.60-4.10(m, 4H,$2CH_2$ester),1.30-1.10(m,6H, CH_3).
4a	3460(OH),3390,3300(NH_2), 1685,1660(2C=O),1620(C=N)	9.5(1H,OH),8.20-8.00(m,2H,arom.) 7.40-7.10(m,3H,arom.),6.50(br,2H, NH_2).
4b	3460(OH),3390,3300(NH_2), 2990,2960(C-H)alif.,1720, 1665(2C=O),1620(C=N)	9.40(1H,OH),6.50(br.2H,NH_2),4.5- 4.10(q,2H,CH_2ester),1.50-1.10, (tr,3H,CH_3)
5a	3230(NH),1685,1665(2C=O) 1600(C=N)	8.90-8.80(1H,NH),7.90-7.50(m,15H, 3H,arom.).
5b	3230(NH),2985-2950(C-H) alif.,1700,1660(2C=O),1600 (C=N)	8.90-8.80(1H,NH),7.90-7.50(m,10H, 2H,arom),4.50-4.10(q,2H,CH_2, ester,1.50-1.20(tr,3H,CH_3).
6a	3148(NH),2995-2975(C-H) alif.,1680,1650(2C=O)	8.90-8.70(1H,NH),7.90-7.40(m,15H, 3H,arom.),6.50-6.40(m,2H,C=H)
6b	3150(NH),2990-2950(C-H) alif.,1705,1660(2C=O)	8.90-8.70(1H,NH),7.95-7.40(m,10H, 2H,arom.),6.60-6.50(m,2H,2 CH).
7	2990-2965(C-H)alif.,1730, (C=O),1600(C=N)	11.50(1H,OH),3.60(br,1H,SH),1.20 (3H,SCH_3).
8	3460(OH),2985-2960(C-H) alif.,1720,1665(C=O),1620 (C=N)	9.40(1H,OH),4.40-3.70(m,4H,Pyrr- yl),3.90-3.60(q,2H,CH_2ester), 1.40-1.10(tr,3H,CH_3).

TABLE II (*Continued*)

comp.	IR(KBr) Cm^{-1}	^{1}H-nmr (DMSO-d_6) ,(δppm)
9	3450,3400(2OH),1730,1680 (2C=O),1620(C=N)	11.50(s,1H,OH),9.50(s,1H,OH), 4.60-4.10(m,4H,Pyrryl).
10	3400(OH),1680,1670(2C=O), 1620(C=N)	9.50(s,1H,OH),4.90-4.40(m,3H, Pyrryl).
11	3420,3230(NH_2),2990-2960 (C-H)alif.,1720,1665(2C=O)	7.50-7.30(br,2H,NH_2)4.50-4.20(m, 4H,Pyrryl),4.00-3.70(q,2H,CH_2est er),3.50(br,1H,SH),1.40-1.10(tr, 3H,CH_3).
12	2990-2955(C-H)alif.,1720, 1685(2C=O),1600(C=N)	8.10-7.80(m,2H,arom.),7.50-7.10 (m,3H,arom.),4.50-4.10(m,4H,Pyrr-yl),3.90-3.50(q,2H,CH_2ester), 1.50-1.10(tr,3H,CH_3).
13	3450(OH),1730,1680(2C=O) 1600(C=N)	11.50(1H,OH),8.10-7.70(m,5H,arom) 4.50-4.10(m,4H,Pyrryl).
14	1680,1670(2C=O),1620(C=N)	8.20-7.90(m,5H,arom.),4.90-4.40 (m,3H,Pyrryl).

Synthesis of 4-amino-3-carbamoyl-2-mercapto-5-(substituted)thiophene 2a,b. A mixture of cyanoacetamide (9.24 g, 0.11 mol) and carbon disulfide (9.00 ml, 0.15 mol) in 40 ml of ammonia solution (28%) was stirred at room temperature for 8 hours. The dithioic ammonium salt (9.7 g, 0.05 mol) was treated with an equivalent amount of α-bromoacetophenone (9.9 g, 0.05 mol) or ethylchloroacetate (5.35 g, 0.05 mol) in aqueous ethanol (200 ml). The reaction mixture was stirred for 2 hours at room temperature where the S-alkylated product was precipitated, filtered off and used in the next step without further purification. (0.05 mol) of compound 1a,b was refluxed with an equivalent amount of sodium ethoxide in ethanol (250 ml) for 4 hours. After cooling the reaction mixture was poured into ice water, acidified with dilute HCl, filtered off, washed with water and recrystallized from the proper solvent.

Synthesis of 4-amino-3-carbamoyl-5-(substituted)-2-thioalkylated thiophene 3a,b. A mixture of compound 2a,b (0.01 mol), ethylchloroformate (0.96 ml, 0.01 mol) and triethylamine (1.39 ml, 0.01 mol) in 20 ml dioxane was stirred at room temperature for one hour. The precipitated product was collected by filtration and recrystallized from the proper solvent.

Synthesis of 5-amino-2-hydroxy-6-(substituted)-thieno(2,3-d)-1,3-thiazin-4-one 4a,b. A mixture of compound 2a,b (0.01 mol), ethylchloroformate (0.96 ml, 0.01 mol) and triethylamine (1.39 ml, 0.01 mol) in 20 ml dioxane was refluxed for 4 hours. The resulting precipitate was collected by filtration and recrystallized from the proper solvent.

Synthesis of 5-benzoylamino-2-phenyl-6-(substituted) thieno(2,3-d)-1,3-thiazin-4-one 5a,b. A mixture of compound 2a,b (5.7 mmol), benzoylchloride (1.4 ml, 11.4 mmol) and triethylamine (1.57 ml, 11.4 mmol) in 25 ml dioxane was refluxed for 4 hours. The resulting precipitate was collected by filtration and recrystallized from the proper solvent.

Synthesis of 5-n-(benzylidine)-2-phenyl-6-(substituted)-2,3-dihydro-thieno(2,3-d)-1,3-thiazin-4-one 6a,b. A mixture of compound 2a,b (8.6 mmol), benzaldehyde (4 g, 37.5 mmol) and 5 ml of 20% H_2SO_4 in

methanol (20 ml) was refluxed for 15 min. The crude precipitate was collected, washed with ethanol. dried and recrystallized from the proper solvent.

Synthesis of 7-carboxy-5-mercapto-2-methyl-thieno(3,2-d)-2,3-oxazin-4-one 7. Compound 2b (2.34 g, 0.01 mol) was refluxed in ethanolic sodium hydroxide solution (50 ml, 12%) for one hour. The precipitated sodium salt was filtered off, washed with alcohol and left to dry. The resulting sodium salt was refluxed for 3 hours with acetic anhydride (20 ml), on cooling the obtained product was filtered off, and recrystallized from the proper solvent.

Synthesis of 2-hydroxy-6-carbethoxy-5(1-pyrryl)-thieno(3,2-d)-1,3-thiazin-4-one 8 *and 6-carbethoxy-2-phenyl-5-(1-pyrryl)-thieno(3,2-d)-1,3-thiazin-4-one* 11. To (0.05 mol) of compound 2b or 4b in (50 ml) glacial acetic acid, (6.5 ml, 0.05 mol) of 2,5-dimethoxytetrahydrofuran was added. The reaction mixture was refluxed for one hour. The cooled reaction mixture was poured into ice water, and the crude precipitate was recrystallized from the proper solvent.

Synthesis of 2-hydroxy-6-carboxy-5-(1-pyrryl)-thieno(2,3-d)-1,3-thiazin-4-one 9 *and 6-carboxy-2-phenyl-5-(1-pyrryl)-thieno(2,3-d)-1,3-thiazin-4-one* 13. (0.01 mol) of compound 8 or 12 was refluxed for one hour in ethanolic sodium hydroxide solution (50 ml, 4%). The cooled section mixture was diluted with water and acidified with dilute HCl. The precipitate was filtered off, and recrystallized from the proper solvent.

Synthesis of 6-carbethoxy-2-phenyl-5-(1-pyrryl)-thieno (2,3-d)-1,3-thiazin-4-one 12. A mixture of compound 11 (2.96 g, 0.01 mol), benzoyl chloride (1.3 ml, 0.01 mol) and triethylamine (1.38 ml, 0.01 mol) in 25 ml dioxane was refluxed for 4 hours. The resulting precipitate was collecting by filtration and recrystallized from the proper solvent.

Synthesis of 2-hydroxy-pyrrolo(2,1-e) pyrrolo(3,2-b)thieno(2,3-d)-1,3-thiazin-4-one 10 *and 2-phenyl-pyrrolo(2,1-e)pyrrolo(3,2-b)thieno(2,3-d)-1,3-thiazin-4 one* 14. To (25 ml) of a cold solution of polyphosphoric acid, (0.005 mol) of compound 9 or 13 was added portionwise and the reaction mixture was then heated for 30 min. After cooling the mixture was added to ice cold water. The separated solid was filtered off, washed with a 5% solution of sodium bicarbonate and then washed with water, dried and recrystallized from the proper solvent.

ACKNOWLEDGEMENT

The author wishes to express his thanks to Prof. Dr. A. K. El-Shafei for his valuable discussions.

REFERENCES

1. A. Thuiller and J. Vialle, *Bull. Chem. Soc. Fr.* (1959).
2. G. Kobayashi, Y. Matsuda and R. Natsuki, *Chem. Pharm. Bull.*, **21,** 921 (1973).
3. R. Gompper and H. Schaefer, *Chem. Ber.*, **100,** 591 (1967).
4. S. Rajappa, R. Sreenivasan, B. G. Advani, R. H. Summer Ville and R. Hoffamann, *Indian. J. Chem. Sect. B.*, **15,** 297 (1977).
5. M. Augustin and W. Doeling, *J. Prakt. Chem.*, **324,** 3 (1982).
6. M. D. Nair, S. Rajappa and J. A. Desai, *Indian J. Chem. Sect. B.*, **21,** 1 (1982).
7. M. D. Naier and J. A. Desai, *Indian. J. Chem. Sect. B.*, **21,** 4 (1982).
8. S. Rajappa, M. D. Nair, R. Sreenivasan and B. G. Advani, *Tetrahedron*, **36,** 1673 (1982).
9. Z.-T. Huang and Z.-R. Liu, *Synthesis*, 357 (1987).
10. R. Gompper and W. Toepfl, *Chem. Ber.*, **95,** 2961 (1962).
11. K. Hirai, H. Matsuda and Y. Kishda, *Chem. Pharm. Bull.*, **20,** 97 (1971).
12. N. B. Mansour, W.-D. Rudorf and M. Z. Augustin, *Chem.*, **21,** 69 (1981).
13. S. Rajappa and B. G. Advani, *Proc. Indian Acad. Sci. (Chem. Sci.)*, **91,** 463 (1982).
14. Z.-T. Huang and X. Shi, *Synthesis*, 162 (1990).
15. J. Sandstrom and I. Wennerbeck, *Acta. Chem. Scand.*, **24,** 1191 (1970).
16. a) I. Gompper and E. Kutter, *Amgew Chem.*, **74,** 251 (1962); b) D. Seebach and R. Burstighaus, *Synthesis*, 461 (1975).
17. A. K. El-Shafei, A. M. M. El-Sagheir, A. Sultan and A. M. Soliman, *Phosphorus, Sulfer, and Silicon*, **72,** 73 (1992).
18. A. K. El-Shafei, H. A. Abdel-Ghany, A. A. Sultan and A. M. M. El-Sagheir, *Phosphorus, Sulfer,*

and Silicon, **73,** 15 (1992).
19. A. K. El-Shafei, A. M. M. El-Sagheir and E. A. Ahmed, *Synthesis*, in press.
20. A. K. El-Shafei, H. S. El-Kashef and A. A. G. Ghattas, *Gazz. Chem. Ital.*, **111,** 409 (1981).
21. A. K. El-Shafei, A. A. Sultan and G. Vernin, *Heterocycles*, **19,** 333 (1982).
22. A. K. El-Shafei, A. A. G. Ghattas, A. A. Sultan, H. S. El-Kashef and G. Vernin, *Gazz. Chem. Ital.*, **112,** 345 (1982).
23. S. Rault, M. Cugnon de Sevricourt, D. Laduree and M. Robba, *Synthesis*, **8,** 586 (1979).
24. S. Rault, M. Cugnon de Sevricourt and M. Robba, *C. R. Acad. Sci. (C)*, **248,** 533 (1977); *ibid.*, **285,** 381 (1977).
25. G. W. H. Cheeseman and S. G. Greenberg, *J. Heterocycl. Chem.*, **16,** 241 (1979).