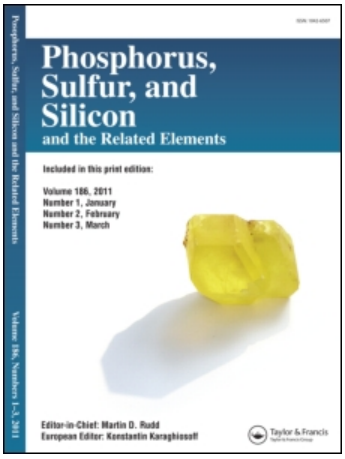


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# Selenium-Containing Heterocycles: Synthetic Investigation of 3-Amino-2-Ethylselenopyridine Carboxylate Using Sodium Borohydride

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# Selenium-Containing Heterocycles: Synthetic Investigation of 3-Amino-2-Ethylselenopyridine Carboxylate Using Sodium Borohydride

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*3-amino-4,6-dimethyl-2-ethylseleno[2,3-b]pyridine carboxylate (**5**) was prepared by a reaction of dipyridyl diselenide derivative (**3**) with sodium borohydride as a reducing agent followed by α-haloester. The reaction of **5** with hydrazine hydrate afforded the corresponding carbohydrazide **8**. The benzylidene derivative **9** provided novel heterocycles of pyrimidoseleno pyridine and thiazinoseleno pyridine derivatives (**10–12**), upon treatment with triethylorthoformate, acetic anhydride, and carbon disulfide, respectively.*

**Keywords** Dipyridyl diselenide; pyrimidoseleno pyridine; seleno[2,3-b]pyridine; thiazinoseleno pyridine



## INTRODUCTION

In recent years, many exciting research results have indicated that selenium is a very important element that has attracted the attention of scientists working in a variety of fields. The interest in selenium-containing compounds has increased not only because of their reactivates and chemical properties[1–5] but also because of their pharmaceutical applications.[6–9] Organ selenium compounds have proven to be an important class of biological active products as antioxidants,[10] antibacterial agents,[11] and catalysts.[12] On the other hand, many pyridines are reported to be useful as herbicides,[13] bactericides,[14] and fungicides,[15] as well as pharmaceuticals.[16] With the goal of using less-toxic selenium compounds for the synthesis of selenium-containing heterocyclic compounds and in continuation of our studies on the preparation of a novel heterocyclic systems containing sulfur and/or selenium

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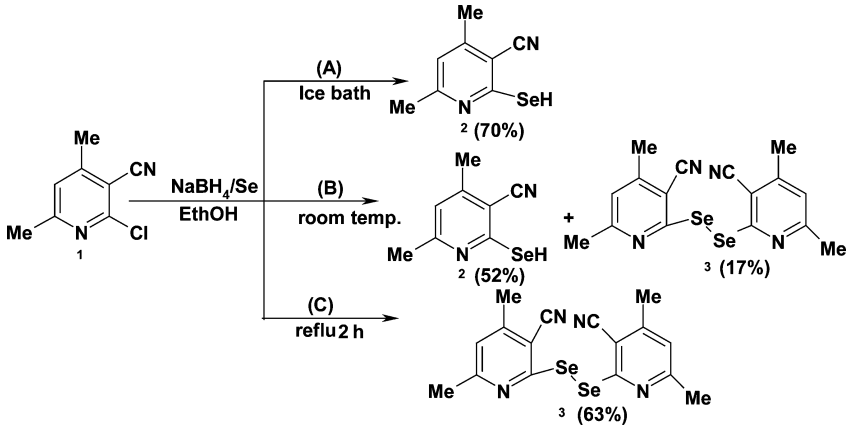
**TABLE I Reaction Condition of $NaBH_4$/Se in Ethanol**

| Reaction condition $NaBH_4$/Se in ethanol | Time (h) | Products/yield % | |
|---|---|---|---|
| | | Compound 2 | Compound 3 |
| (A) Ice bath | 24 | 70 | — |
| (B) Rt | 7 | 52 | 17 |
| (C) Reflux | 2 | — | 63 |

atoms,[17–20] the present article describes the synthesis of new heterocycles on the basis of the seleno[2,3-b]pyridine derivative (**5**).

## RESULTS AND DISCUSSION

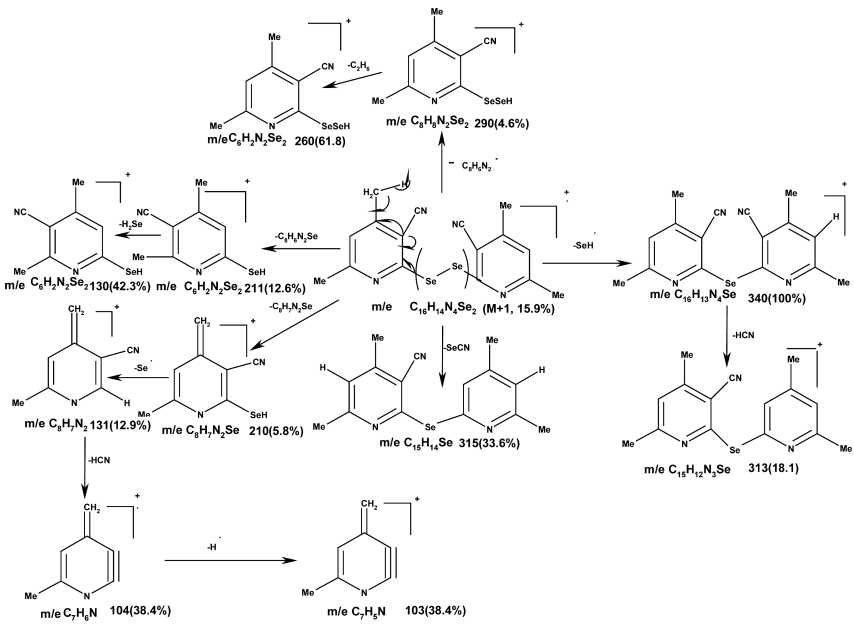
It was reported that 4,6-dimethyl-3-cyanopyridine-2(1H) selenone (**2**) was obtained in a (67%) yield by the reaction of 4,6-dimethyl-2-chloro-3-cyanopyridine (**1**) with sodium hydrogen selenide[21] under reflux. In order to improve the yields and to investigate the synthesis of the title compound **5**, we decided to modify the procedure as follows: first, when the reaction was carried out in an ice bath, we got 4,6-dimethyl-3-cyanopyridine-2(1H) selenone **2** in a good yield (70%); second, at r.t. we obtained compound **2** and new compound 2′,2-bis(3-cyano-4,6-dimethyl)dipyridyl diselenide (**3**) in low yield. The two compounds **2** and **3** were isolated by fractional crystallization from ethanol. Upon recrystallization, compound **2** crystallized from ethanol as yellow crystals, while compound **3** crystallized from dioxan as red crystals. Under reflux, only the dipyridyl diselenide derivative, **3**, was obtained (Table I, Scheme 1).




**SCHEME 1**

The two prepared compounds **2** and **3** were characterized by chemical and spectral data.

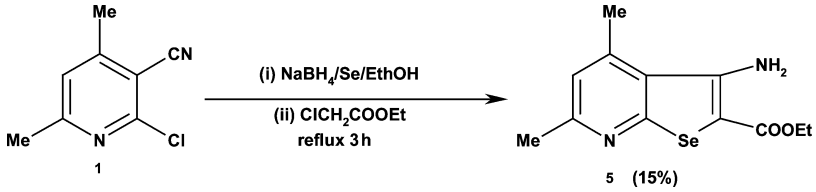
From Scheme 1, it was clear that the natural oxidation of a selenol into diselenide can be accelerated by air and heating.[22] The structure elucidation of 2′,2-bis(3-cyano-4,6-dimethyl)dipyridyl diselenide **3** was confirmed by elemental analysis, IR, $^1$H NMR, and mass spectra. Mass spectra indicate that the presence of molecular ion m/e 420 (14.5%) and 421 (15.9%) with a low relative abundance reflects the instability of this molecular ion under electron impact. The molecular ion underwent extensive skeletal rearrangement to give several fragment ions (Scheme 2).




**SCHEME 2**

On the other hand, attempts to synthesize the title compound **5** in a one-pot reaction using the starting compound **1** and sodium borohydride followed by $\alpha$-haloester leads only to the compound **5** in a low yield (15 %) (Scheme 3).

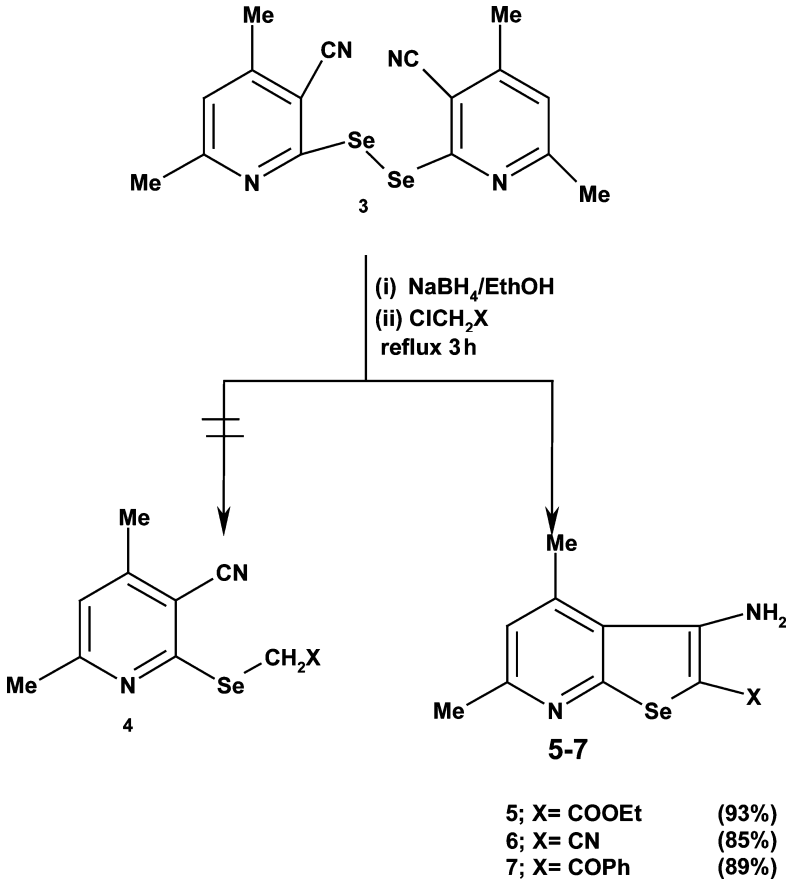
Another new synthetic pathway to improve the overall reaction yield of the target compound **5** is the treatment of the dipyridyl diselenid **3** with sodium borohydride followed by the addition of $\alpha$-haloester under a reflux condition. The expected ethylseleno ester derivative (**4**) was not detected (Scheme 4), and this is may be attributed the double function of



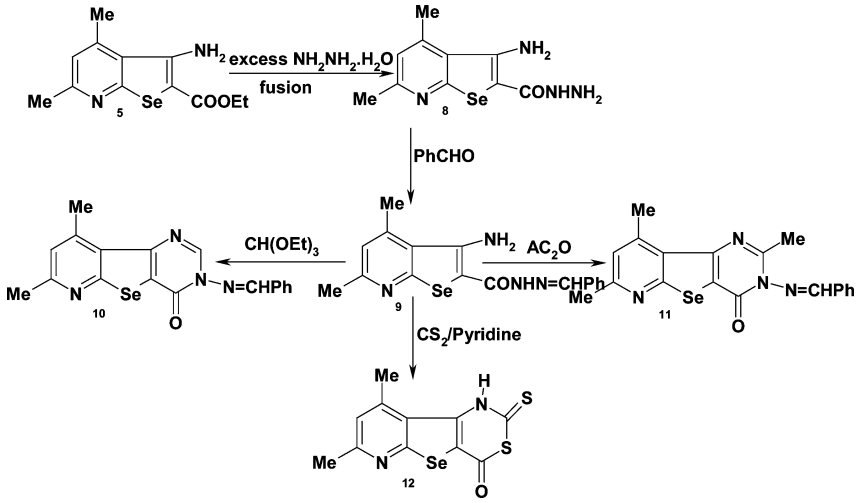

**SCHEME 3**

$NaBH_4$ as a reducing agent and a basic catalyst to furnish the cyclized product **5**.

By the same way, compounds **6** and **7** were prepared. Synthesized compounds **5–7** had nearly identical spectral data as the reported compounds.[21]




**SCHEME 4**




**SCHEME 5**

Further reactions of 3-amino-2-ethylseleno[2,3-b]pyridine carboxylate **5** with hydrazine hydrate, aromatic aldehyde, and carbon disulfide provides novel selenium containing heterocycles as follows: When **5** was allowed to react with hydrazine hydrate by fusion, it gave the corresponding carbohydrazide (**8**), while reflux in ethanol failed. Refluxing compound **8** with benzaldehyde in an equimolar ratio gave benzylidene carbohydrazone (**9**). A new series of pyrimidoseleno pyridine derivatives **10** and **11** were synthesized via the reaction of compound **9** with triethylorthoformate and acetic anhydride, respectively. Refluxing **9** with carbon disulfide in pyridine for a long time gave 2,4-dimethyl-8-oxo[1.3]thiazino[2′,3′:4,5]seleno[2,3-b] Pyridine-6(5H)-thion (**12**) (Scheme 5).

## CONCLUSION

New series of seleno pyridine, pyrimidoseleno pyridine, thiazinoseleno pyridine derivatives were synthesized from 3-cyanopyridine-2(1H)selenone (2). Modification of a literature procedure to prepare selenopyridino derivatives was done with improving the yield.

## EXPERIMENTAL

Melting points were determined using a Kofler melting point apparatus and are uncorrected. IR spectra were recorded on a Pye-Unicam

SP3-100 instrument in KBr. $^1$H NMR spectra were obtained on a JNM-LA spectrometer (400 MHz) using tetramethylsilane as an internal reference. The instrument for measuring mass spectra was JEOL JMS600. Elemental analyses were obtained on a Perkin-Elmer 240 C analyzer; the results coincided with the calculated values within ±0.4%. The progress of reactions and purity of products were monitored by TLC.

## 4,6-Dimethyl-3-cyanopyridine-2(1H)selenones (2; $C_8H_8N_2Se$) and 2′,2-Bis(3-cyano-4,6-dimethyl)dipyridyldiselenide (3; $C_{16}H_{14}N_4Se_2$)

The modified procedures are as follows:



### *Procedure A*

4,6-dimethyl-2-chloro-3-cyanopyridine 1(1 mmoles) was added stepwise in a mixture of selenium metal (1 g, 12 mmoles) and sodium borohydride (1.2 g, 32 mmoles) in ethanol. The reaction mixture was stirred in ice bath for 24 h; then the reaction mixture was poured onto an ice water and acidified by conc. hydrochloric acid. The precipitate was isolated by filtration, washed with water, and recrystallized from ethanol to give compound **2** as yellow crystals, yield 0.9 g (70%) (reported 67%). The melting point and all spectral data were in agreement with the reported compound.[21]

### *Procedure B*

Using the same procedure was used as in A, but with stirring for 7 h at r.t. we got compound **2** in a yield of 0.66 g (52%) and 2′,2-bis(3-cyano-4,6-dimethyl) dipyridyl diselenide **3** as red crystals with a yield 0.44 g (17%) (Table I).

### *Procedure C*

The same procedure was used as in A and B, but the reaction mixture was refluxed for 2 h. This gave compound **3**, which was recrystallized from dioxan as red crystals, a yield of 1.57 g (63%). Anal. calcd. for $C_{16}H_{14}N_4Se_2$: C, 45.71; H, 3.33; N, 13.33. Found: C, 45.31; H, 3.00; N, 13.03. IR: $\nu = 2200$, 1575 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$), $\delta$ : 2.41(s, 6H); 2.49 (s, 6H); 7.26 (s, 2H-CH-pyridine) ppm. MS: m/z (%) = 421 [M + 1] (15.9%), 420 [M$^+$] (14.5%), 340 (100), 315 (33.6), 313 (18.1), 290 (4.6), 260 (61.8), 211 (12.6), 131 (12.9), 130 (42.3), 210 (5.8), 105 (1.8), 104 (38.4), 103 (38.4).

## 3-Aminoseleno[2,3-b]pyridine derivatives (5;$C_{12}H_{14}N_2O_2e$), (6; $C_{10}H_9N_3Se$) and (7; $C_{16}H_{14}N_2OSe$) from compound 3

### *General Procedure*

To a solution of **3** (1 g, 2.3 mmoles) in 15 mL of ethanol, sodium borohydride to an ethanolic solution of 3 (1 g, 2.3 mmoles) was added in small portions (0.2 g, 7.0 mmoles). The reaction mixture was stirred at r.t. for 1 h; then 2.3 mmoles of chloro ethylacetate or chloro acetonitrile or benzoyl chloride should be added instead of halo ester or alkyl halide. The resulting mixture was refluxed for 3 h and then poured onto an icewater. The precipitated compounds were collected as follows:

Compound **5**: yield 0.65 g (93%) (reported 88%);
Compound **6**: yield 0.5 g (85%) (reported 76%); and
Compound **7**: yield 0.70 g (89%) (reported 81%).

m.p.s. and all spectral data were in agreement with those of the reported compounds.[21]



## 3-Amino-4,6-dimethyl-2-ethylseleno[2,3-b]pyridine Carboxylate (5;$C_{12}H_{14}N_2O_2Se$) from Compound 1

To a suspension of selenium metal (1 g, 12 mmoles) in 15 mL of ethanol (1.2 g, 32 mmoles) of sodium borohydride was added in small portions, and then the corresponding 2-chloro-3-cyanopyridine derivative **1** (1.66 g, 10 mmoles) was added in small portions. The reaction mixture was stirred in an ice bath for 7 h, and then $\alpha$-haloester (1.22 g, 10 mmoles) was added. After that the reaction mixture was refluxed for 3 h, cooled, and poured onto cold water, followed by acidification with conc. hydrochloric acid. The product was collected in a low yield, 0.45 g (15%). Spectra of **5** were in agreement with earlier measurements.[21]

## 3-Amino-4,6-dimethylseleno[2,3-b]pyridine-2-carbohydrazide (8; $C_{10}H_{12}N_4OSe$)

A mixture of the selenopyridine derivative **5** (2 g, 4.7 mmoles) and hydrazine hydrate (5 mL, 85%) was fused together for 5 h. The hot solid product was separated by filtration, washed well with ethanol, and recrystallized from dioxan as yellow crystals, m.p. $> 300^\circ$C, yield 1.6 g (84%). calcd. for $C_{10}H_{12}N_4OSe$: C, 42.40; H, 4.24; N, 19.78. Found: C, 42.01; H, 3.93; N, 19.47. IR: $\nu = 3100, 3195, 3290$ cm$^{-1}$ ($NHNH_2$); 1620 cm$^{-1}$. $^1$H NMR ($CDCl_3$), $\delta$: 2.41 (s, 3H); 2.52 (s, 3H); 4.5 (s,2H,$NH_2$-hydrazide); 6.01 (s, 2H, $NH_2$-attached to selenophene ring); 7.09 (s, 1H); 7.4 (1H, NH) ppm.

### 3-Amino-2-benzyledine Carbohydrazone-4,6-dimethylseleno-[2,3-b]pyridine(9); $C_{17}H_{16}N_4$ OSe)

A mixture of selenopyridine carbohydrazide **8** (2.83 g, 10 mmoles), benzaldehyde (1.06 g, 10 mmoles) in 30 mL of ethanol, and 2 drops of piperidine was refluxed for 3 h. It was then allowed to cool. The solid product was collected and recrystallized from dioxan, m.p. > 300°C, yield 3 g (81%). calcd. for $C_{17}H_{16}N_4OSe$: C, 54.98; H, 4.31; N, 15.09. Found: C, 54.59; H, 4.13; N, 14.88. IR: $\nu$ = 3450, 3300, 3170 ($NH_2$) ; 1625 (C=O) $cm^{-1}$. $^1$H NMR (DMSO-$d_6$), $\delta$ : 2.40 (s, 3H); 2.62 (s, 3H); 6.82 (s,2H, $NH_2$); 7.17 (s, 1H), 8.5 (s, 1H, N=CH); 9.20 (s, 1H, NH) ppm.

### 2,4-Dimethyl-7-benzyledineamino-8-oxopyrimido[4′,5′:4,5]-seleno[2,3-b]pyridine (10; $C_{18}H_{14}N_4OSe$)



To a mixture of **9** (1 g, 2.7 mmoles) and triethylorthoformate (5 mL), drops of acetic acid (5 drops) were added. The reaction mixture was heated under reflux for 1 h. The solid product was collected and recrystallized from acetic acid, m.p. > 300°C, yield 0.52 g (51%). calcd. for $C_{18}H_{14}N_4OSe$: C, 56.69; H, 3.67; N, 14.69. Found: C, 56.37; H, 3.38; N, 14.29. IR: $\nu$ = 1670 (C=O); 1610 (C=N) $cm^{-1}$. $^1$H NMR (DMSO-$d_6$), $\delta$ : 2.39 (s, 3H); 2.65 (s, 3H); 7.06 (s, 1H); 7.30–7.70 (m, 5H, Ar-H); 8.5 (s,1H, N=CH); 9.30 (s, 1H, CH-pyrimidine) ppm.

### 2,4,6-Trimethyl-7-benzyledineamino-8-oxopyrimido[4′,5′:4,5]-seleno[2,3-b]pyridine (11; $C_{19}H_{16}N_4OSe$)

Compound **9** (0.5 g, 1.3 mmoles) was heated in 10 mL of acetic anhydride under reflux for 6 h and then allowed to cool. The solid product was filtered and recrystallized from acetic acid, m.p. > 300°C, yield 0.3 g (56%). Calcd. for $C_{19}H_{16}N_4OSe$ : C, 57.72; H, 4.05; N, 14.17. Found: C, 57.44; H, 3.89; N, 13.95. IR: $\nu$ = 1680 (C=O); 1600 (C=N) $cm^{-1}$.

### 2,4-Dimethyl-8-oxo-[1.3]thiazino[2′,3′:4,5]seleno[2,3-b]-pyridine-6(5H)-thion (12; $C_{11}H_8N_2OS_2Se$)

A mixture of **9** (2 g, 5.4 mmoles) and carbon disulfide (2 mL) in pyridine (20 mL) was heated on a water bath for 3 days and then allowed to cool, the solid product was collected and recrystallized from dioxan, m.p. = 265–267°C, yield 1.2 g (68 %). calcd. for $C_{11}H_8N_2OS_2Se$: C, 40.36; H, 4.89; N, 8.56; S, 19.57. Found: C, 40.01; H, 4.58; N, 8.34; S, 19.29. IR: $\nu$ = 33100 (NH);1685 (C=O) $cm^{-1}$. $^1$H NMR (DMSO-$d_6$), $\delta$ : 2.43 (s, 3H); 2.52 (s, 3H); 7.09 (s, 1H); 9.2 (s, 1H) ppm.

## REFERENCES


[1] G. L. Sommen, A. Linden, and H. Heimgartner, *Helv. Chim. Acta*, **88,** 766–773 (2005).

[2] D. L. Klayman and W. H. H. Gunther, In *Organic selenium compounds: Their chemistry and biology*, p. 579 and 629 (John Wiley & Sons, New York, 1973).

[3] C. Paulmier, *Selenium reagent and intermediates in organic synthesis*, p. 70, Pergamon Press, Oxford (1986).

[4] M. Renson, *The chemistry of organic selenium and tellurium compounds*, Vol. 1, Eds. S. Patai and Z. Rappoport, p. 339 (John Wiley & Sons, New York, 1986).

[5] V. P. Litvinov and V. D. Dyachenko, *Russ. Chem. Rev.*, **66,** 923 (1997).

[6] R. A. Passwaters, *Selenium as food & medicine* (Pivot Original Press, New Canaan, 1980).

[7] A. Wendel, Ed., *Selenium in biology and medicine* (Springer Verlag, Berlin, 1989).

[8] R.f. burk, *Selenium in biology and human health* (Springer, New York, 1994).

[9] S. Janzsu, G. Hoppert, J. Shodiere, and J. C. Yerdon, JP 1140067 (1999), *Chem. Abstr.*, **131,** 32054 (1999).

[10] G. Mugesh, W. W. Du Mont, and H. Sies, *Chem. Rev.*, **101,** 2125 (2001).

[11] E. V. Ratushnaya, Y. I. Kirova, M. A. Suchkov, B. I. Drevko, and V. B. Borodulin, *J. Chem. Pharm.*, **36,** 652 (2002).

[12] C. Jacob, G. Giles, and F. Fry, US Pat wo 200 4047925 (2004).

[13] T. Maier, S. Scheiblich, and H. S. Baltruschat, US Pat 11 064 (2001); *Chem. Abstr.*, **135,** 13344ow (2001).

[14] S. A. Armstrong, J. M. Berge, P. Brown, J. S. Elder, A. K. Forrest, O. W. Hamprecht, and R. L. Jarrest, PCT Int. Appl. WO 0071 524 (1999); *Chem. Abstr.*, **134,** 17496 (2001).

[15] Proctor and Gamble Ltd., US Pat. 3 236733 (1966); *Chem. Abstr.*, **64,** 17364 (1966).

[16] Rasching, US Pat. 2 937 118 (1960); *Chem. Abstr.*, **54,** 17807 (1966).

[17] Sh. H. Abdel-Hafez, *Phosphorous, Sulfur, and Silicon*, **178,** 2563–2579 (2003).

[18] Sh. H. Abdel-Hafez, *Russian J. of Organic Chemistry*, **41,** 396–401 (2005).

[19] M. A. Abbady, Sh. H. Abdel-Hafez, M. M. Kandeel, and M. I. abdel-Monem, *Molecules*, **8,** 622–641 (2003).

[20] M. A. Abbady and Sh. H. Abdel-Hafez, *Phosphorous, Sulfur, and Silicon*, **160,** 121–139 (2000).

[21] P. Litvinov, V. Yu. Mortikov, Yu. A. Sharanin, and A. M. Shestopalov, *Synthesis*, **1,** 98–99 (1985).

[22] A. Toshimitsu H. Owada, K. Terao, and S. Uemura and M. Okano *J. Organic Chem.*, **49,** 3796–3800 (1984).