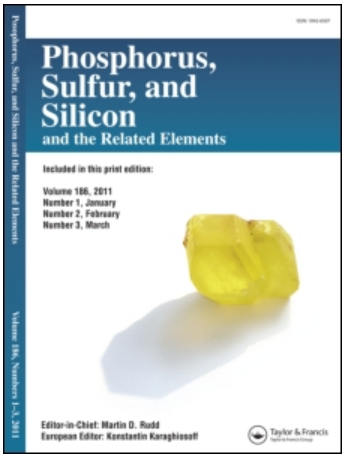


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

REACTION OF SUBSTITUTED BENZAMIDE OXIMES WITH CHLOROACETYL CHLORIDE AND THIOPHOSGENE

Hkmet Ağibaş[a]; Ayşle Gül Kaya[a]; Murat Aydoğdu[a]
[a] Department of Chemistry, Kocaeli University, İzmit, Turkey

To cite this Article Ağibaş, Hkmet , Kaya, Ayşle Gül and Aydoğdu, Murat(1999) 'REACTION OF SUBSTITUTED BENZAMIDE OXIMES WITH CHLOROACETYL CHLORIDE AND THIOPHOSGENE', Phosphorus, Sulfur, and Silicon and the Related Elements, 149: 1, 39 — 48
To link to this Article: DOI: 10.1080/10426509908037021
URL: http://dx.doi.org/10.1080/10426509908037021

Phosphorus, Sulfur and Silicon, 1999, Vol. 149, pp. 39-48
Reprints available directly from the publisher
Photocopying permitted by license only

REACTION OF SUBSTITUTED BENZAMIDE OXIMES WITH CHLOROACETYL CHLORIDE AND THIOPHOSGENE

HİKMET AĞIRBAŞ *, AYŞE GÜL KAYA and MURAT AYDOĞDU

Department of Chemistry, Kocaeli University, 41300 İzmit, Turkey

(Received 14 December, 1998)

3,4-Disubstituted-5,6-dihydro-4H-1,2,4-oxadiazine-5-ones were obtained from the reaction of substituted benzamide oximes with chloroacetyl chloride. The thionation of these compounds gave the corresponding 5-thiones. 3,4-Disubstituted-1,2,4-oxadiazole-5(4H)-thiones were obtained from the reaction of substituted benzamide oximes with thiophosgene. The copper-catalysed rearrangement of these compounds gave the isomeric 1,2,4-thiadiazole-5-ones.

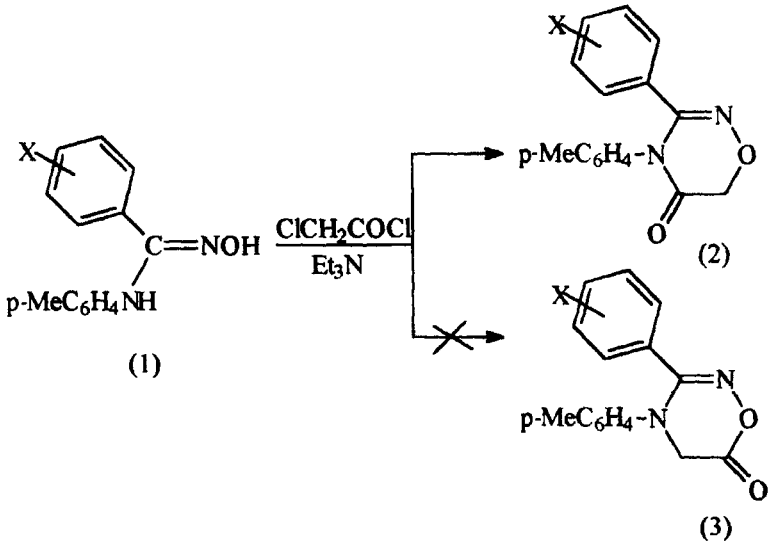
Keywords: 1,2,4-Oxadiazine-5-one; 1,2,4-oxadiazine-5-thione; 1,2,4-oxadiazole-5-thione; 1,2,4-thiadiazole-5-one

In our preliminary communication[1], we caused N-Methylbenzamide oximes to react with chloroacetyl chloride and obtained 3-phenyl-4-methyl-5,6-dihydro-4H-1,2,4-oxadiazine-5-one, rather then 3-phenyl-4-methyl-5,6-dihydro-4H-1,2,4-oxadiazine-6-one. For comparison, the 1,2,4-oxadiazine-5-one was also obtained[1] from the reaction of N-methyl benzamide oxime with ethyl chloroacetate.

In this study, we caused N-(p-tolyl)-substituted benzamide oximes (1a-c) to react with chloroacetyl chloride and in each case we obtained only one product (compound 2)(Scheme 1).

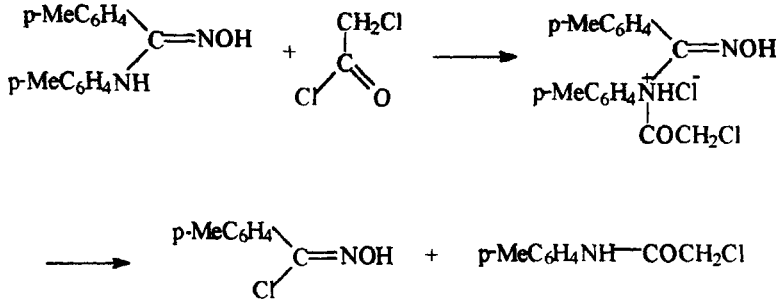
The reaction of N-(p-tolyl)-p-methylbenzamide oxime (1c) with chloroacetyl chloride also gave N-(p-tolyl)chloroacetamide along with 3,4-di(p-tolyl)-5,6-dihydro-4H-1,2,4-oxadiazine-5-one (2c). The mechanism for the formation of N-(p-tolyl)chloroacetamide could be considered as shown below (Scheme 2).

* Correspondence Author.



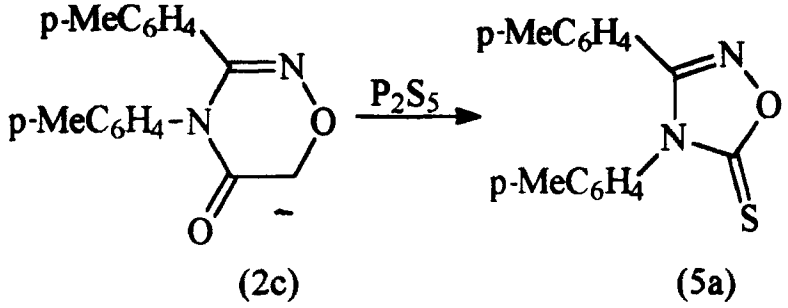
X: a; H, b; p-Cl, c; p-Me

SCHEME 1



SCHEME 2

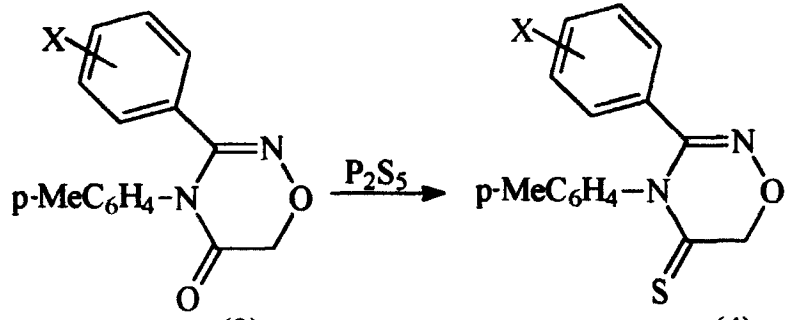
The treatment of compound (2c) with P_2S_5 gave a compound which was found to be identical in all respects with 3,4-di(p-tolyl)-1,2,4-oxadiazole-5-(4H)-thione (5a) (Scheme 3).



(2c) (5a)

SCHEME 3

The thionation of compounds (2a-b) with P_2S_5 gave the corresponding 5-thiones (4a-b) (Scheme 4).



(2) (4)

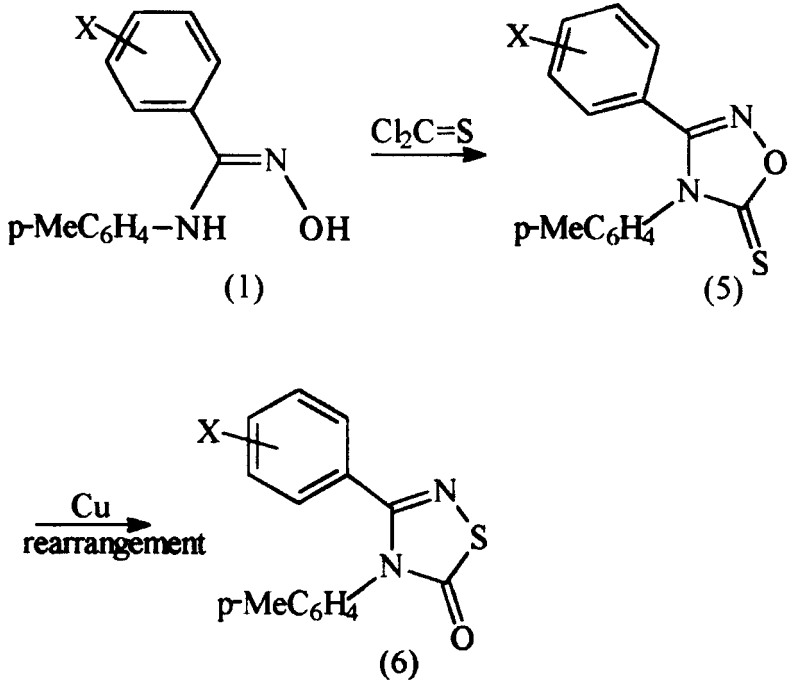
X: a; H, b; p-Cl

SCHEME 4

Compound (4a-b) were heated for 5h at 250°C in diphenyl ether with and without the presence of a catalytic amount of copper powder and any rearrangement or decomposition was not observed, however, acyclic or heterocyclic compounds which have a O-C=S group generally rearrange to S-C=O or decompose at this temperature[2-13]. Therefore, the stability of compound (4) indicates that these compounds are 1,2,4-oxadiazine-5-thiones, and not 1 ,2,4-oxadiazine-6-thiones.

Derivatives of 1,2,4-oxadiazole-5-thiones and 1,2,4-thiadiazole-5-ones are of interest from the pharmacological point of view[14]. We have previously studied[2,3] the preparation and the copper-catalysed rearrangement of some derivatives of 1,2,4-oxadiazole-5-thiones. We now report here further study on the synthesis and the copper-catalysed rearrangement of 1,2,4-oxadiazole-5-thiones carring functional groups such as CH_3, NO_2, Cl and CN.

The compounds (5a-d) were prepared from the reaction of substituted benzamide oximes with thiophosgene (Scheme 5).



X: a; p-Me, b; p-Cl, c; m-NO_2, d; p-CN

SCHEME 5

When the compounds (5a and 5c) were heated for 6h at 180°C in diphenylether in the presence of a catalytic amount of copper powder, these com-

pounds were converted into compounds (6a and 6c)(Scheme 5). When compound (5b) was submitted to the same treatment, it was found that it decomposed. This compound was successfully rearranged to compound (6b) in xylene at reflux temperature in 16h in the presence of a copper catalyst. On the other hand, when compound (5d) was heated in xylene or diphenylether in the presence of copper powder, it failed to rearrange to compound (6d). In both solvents, compound (5d) seemed to be decomposed.

EXPERIMENTAL

^{1}H NMR spectra were taken on a Brucker AC 200-L(200MHz) spectrometer, mass spectra on a VCZAP SPEC instrument, and IR spectra on a Simadzu FTIR-821PC Fourier Transform IR spectrometer. Silica Gel HF_{254} was used for preparative thin layer chromatography. Solvents used as reaction media or as eluents were dried and purified by standard methods prior to use. Melting points were determined on a Büchi apparatus and are uncorrected.

N-Substituted benzamide oximes were prepared from the reaction of hydroxamic acid chloride with primary amines as described in the literature[15,16].

3-Phenyl-4(p-tolyl)-5,6-dihydro-4H-1,2, 4-oxadiazine-5-one (2a)

A solution of chloroacetyl chloride (289mg, 2.64mmol) in chloroform (5ml) was added dropwise to a solution of N-(p-tolyl)benzamide oxime (400mg, 1.76mmol) and triethylamine (445mg, 4.4mmol) in chloroform (15ml). The reaction mixture was stirred for 6 days at room temperature. Solvent was evaporated under reduced pressure. The remaining solid material was extracted with acetone. The solvent was evaporated and the crude product was recrystallized from ether-light petroleum (50–70°C) (1: 2) to give compound **(2a)** (250mg, 53%), m.p. 96–98°C. IR(KBr): υ = 1725cm^{-1} (C=O), 1599, 1566(C=N). ^{1}H NMR(CDCl): δ=2.26(s, 3H, CH_3), 4.64(, 2H, CH_2), 7.09(m, 4H, aromatic H), 7.14–7.22(m, 5 aromatic H). MS(70eV); m/z(%): 266(100)[M^+]. Found: C, 72.81; H, 5.14; N, 10.52. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.20; H, 5.30; N, 10.52.

3-(p-Chlorophenyl)-4-(p-tolyl)-5,6-dihydro-4H-1,2, 4-oxadiazine-5-one (2b)

A solution of chloroacetyl chloride (2.5g, 22.16 mmol) in benzene (3ml) was added dropwise to an ice-cooled solution of N-(p-tolyl)-p-chlorobenzamide oxime (3.85g, 14.7mmol) and triethylamine (3.73g, 36.9mmol) in benzene (45ml). An immediate precipitation was observed. The reaction mixture was stirred for 6 days at room temperature. The precipitate was filtered off. Benzene was evaporated under reduced pressure. The remaining oily product was crystallized from benzene: n-hexane (1:1) to give compound **(2b)** (1.28g, 28%), m.p. 102–104°C. IR(KBr). υ=1676cm^{-1}(C=O), 1556, 1512(C=N). ^{1}H NMR(CDCl): δ=2.29(s, 3H, CH_3), 4.63(s, 2H, CH_2), 7.00(m, 2 aromatic H), 7.12(m, 2 aromatic H), 7.18(m, 2 aromatic H, 7.22(m, 2 aromatic H). MS(70eV); m/z(%): 300(86)[M$^+$].

3,4-Di(p-tolyl)-5,6-dihydro-4H-1,2,4-oxadiazine-5-one (2c)

A solution of chloroacetyl chloride (229mg, 1.35mmol) in benzene(5ml) was added dropwise to an ice-cooled solution of N-(p-tolyl)-p-toluamide oxime (325mg, 1.35mmol) and triethylamine(341.5mg, 3.37mmol) in benzene(25ml). The reaction mixture was stirred for 6 days at room temperature. The precipitate was filtered off. Benzene was evaporated under reduced pressure. The remaining oily residue was subjected to thin layer chromatography (eluent, ethanol: chloroform: n-hexane)(1:1:5) to yield compound **(2c)** (30mg, 15%, R_f=0.56) and N-(p-tolyl)chloroacetamide (20mg, 17%, R_f=0.60).

(2c): m.p. 122–124°C. IR(KBr): υ=1732cm^{-1}(C=O), 1590(C=N). ^{1}H NMR($CDCl_3$): δ=2.31(s, 6H, $2CH_3$), 4.62(s, 2H, CH_2), 7.01(m, 6 aromatic H), 7.17(m, 2 aromatic H). MS(70 eV); m/z(%): 280(98)[M$^+$].

N-(p-tolyl)chloroacetamide

IR(KBr): υ=1670cm^{-1}(C=O), 3274(N-H). ^{1}H NMR($CDCl_3$). δ=2.33(s, 3H, CH_3), 4.18(s, 2H, CH_2), 7.18(m, 2 aromatic H), 7.4(m, 2 aromatic H). MS(70 eV); m/z(%): 183(94)[M$^+$].

3-Phenyl-4-(p-tolyl-5,6-dihydro-4H-1,2,4-oxadiazine-5-thione (4a)

General Procedure

Compound (**2a**) (210mg,) was refluxed with P_2S_5 (90mg, 0.39mmol) in xylene for 12h. The reaction mixture was filtered and xylene was evaporated under reduced pressure. The remaining oily residue was subjected to tlc (eluant, ethyl acetate: n-hexane)(2: 3) to yield an oily compound (**4a**) (85mg, 39%, R_f=0.79). IR(KBr): υ=1560cm^{-1}(C=N), 1338(C=S). ^{1}H NMR($CDCl_3$): δ=2.25(s, 3H, CH_3), 4.88(s, 2H, CH_2), 7.18(m, 4 aromatic H), 7.24(m, 5 aromatic H). MS(70eV); m/z(%): 283(77)[M^+]. Found: C, 67.93; H, 5.33; N, 9.62, Calcd. for $C_{16}H_{14}N_2OS$: C, 68.05; H, 4.99; N, 9.31.

3-(p-Chlorophenyl)-4-(p-tolyl)-5,6-dihydro-4H-1,2,4-oxadiazine-5-thi one (4b)

Compound (**2b**) was thionated as described above and the product was chromatographed on Silica Gel HF_{254} layer with ethyl acetate: n-hexane (1:3)(R_f: 0.64) to give compound (**4b**), m.p. 146–148°C. IR(KBr): υ=1600cm^{-1}(C=N), 1344(C=S). ^{1}H NMR($CDCl_3$): δ=2.29(s, 3H, CH_3), 4.87(s, 2H, CH_2), 7.17(m, 2 aromatic H), 7.20(m, 2 aromatic H), 7.24(m, 4 aromatic H). MS(70eV); m/z(%). 316(61)[M^+].

Treatment of 3,4-Di(p-tolyl)-5,6-dihydro-4H-1,2,4-oxadiazine-5-one (2c) with P_2S_5

Compound (**2c**) (80mg, 0.285mmol) was refluxed with P_2S_5 (31.7mg, 0.14mmol) in xylene for 13h. The mixture was filtered and xylene was evaporated under reduced pressure. The residue was subjected to tlc (eluant, ethyl acetate: n-hexane)(1:1) to yield the compound (30mg, 35%, R_f=0.52) which was found to be identical in all respects with compound (**5a**).

3,4-Di(p-tolyl)-1,2,4-oxadiazole-5(4H)-thione (5a).

General Procedure

Thiophosgene (1mmol, 121mg) was added to an ice-cooled solution of N-(p-tolyl)-p-toluamide oxime (1mmol, 241mg) in pyridine (2ml). The

reaction mixture was stirred for 20 min. and poured into cold water (50ml). The resulting precipitate was filtered and washed with water. After crystallization from ethanol, the IR spectrum of the product gave a C=O absorption at ~1770cm^{-1}. The impure solid was refluxed with an excess of P_2S_5 in xylene for 12h. The reaction mixture was filtered and the solvent was evaporated under reduced pressure. The remaining oily residue was recrystallized from ethanol, yielding compound (5a)(100mg, 35%), m.p. 157–159°C. IR(KBr): υ=1610cm^{-1}C=N), 1350(C=S). ^{1}H NMR($CDCl_3$): δ=2.35(s, 3H, CH_3), 2.42(s, 3H, CH_3), 7.13–7.32(m, 8 aromatic H). MS(70eV); m/z(%): 282(100)[M^+]. Found: C 67.58; H, 5.03; N, 9.81, Calcd. for $C_{16}H_{14}N_2OS$: C, 68.09; H, 4.96; N, 9.92.

3-(p-Chlorophenyl)-4-(p-tolyl)-1,2,4-oxadiazole-5(4H)-thione (5b)

M.p. 168–170°C. IR(KBr): υ=1604cm^{-1}(C=N), 1340(C=S). ^{1}H NMR($CDCl_3$): δ=2.43(s, 3H, CH_3), 7.15(m, 2 aromatic H), 7.30(m, 6 aromatic H). MS(70eV); m/z(%): 302(62)[M^+]. Found: C, 59.59; H, 3.81; N, 9.34, Calcd. for $C_{15}H_{11}N_2ClOS$: C, 59.52; H, 3.63; N, 9.25.

3-(m-Nitrophenyl)-4-(p-tolyl)-1,2,4-oxadiazole-5(4H)-thione (5c)

M.p. 161–163°C; IR(KBr): υ=1610cm^{-1}(C=N), 1350(C=S). ^{1}H NMR($CDCl_3$): δ=2.44(s, 3H, CH_3), 7.19(d, 2 aromatic H), 7.35(d, 2 aromatic H), 7.62(m, 1 aromatic H, 7.73(d, 1 aromatic H), 8.21(s, 1 aromatic H), 8.35(d, 1 aromatic H) MS(70eV); m/z(%): 313(100)[M^+]. Found: C, 57.49; H, 3.73; N, 12.74, Calcd. for $C_{15}H_{11}N_3O_3S$: C, 57.52; H, 3.51; N, 13.41.

3-(p-Cyanophenyl)-4-(p-tolyl)-1,2,4-oxadiazole-5(4H)-thione (5d)

M.p. 174–176°C. IR(KBr): υ=2231 cm^{-1}(C≡N), 1590(C=N), 1340(C=S). ^{1}H NMR($CDCl_3$): δ=2.44(s, 3H, CH_3), 7.16(d, 2 aromatic H), 7.33(d, 2 aromatic H), 7048(d, 2 aromatic H), 7.66(d, 2 aromatic H). MS(70eV); m/z(%): 293(100)[M^+]. Found: C, 65.35; H, 3.98; N, 13.92, Calcd. for $C_{16}H_{11}N_3OS$: C, 65.53; H, 3.75; N, 14.32.

3,4-Di(p-tolyl)-1,2,4-thiadiazole-5(4H)-one (6a)

Compound **(5a)** (200mg) was heated in diphenyl ether (0.5ml) in a tube for 6h at 180°C in the presence of a catalytic amount of copper powder. After cooling, diethyl ether was added to the mixture and filtered. Diethyl ether was evaporated and the residue was first washed with petroleum ether (50–70°C) then recrystallized from ethanol, yielding compound **(6a)**(120mg, 60%), m.p. 167–169°C. IR(KBr); υ=1681 cm^{-1}(C=O), 1610((C=N). ^1H NMR($CDCl_3$): δ=2.31(s, 3H, CH_3), 2.40(s, 3H, CH_3), 7.06(m, 4 aromatic H), 7.22(m, 4 aromatic H). MS(70eV), m/z(%): 282(51)[M^+]. Found: C, 67.75; H, 5.18; N, 9.84, Calcd. for $C_{16}H_{14}N_2OS$: C, 68.09; H, 4.96; N, 9.92.

3-(p-Chlorophenyl)-4-(p-tolyl)-1,2,4-thiadiazole-5-one (6b)

Compound **(5b)** (100mg) was heated in xylene(25ml) at reflux temperature in the presence of a catalytic amount of copper powder. The reaction mixture was filtered and the solvent was evaporated under reduced pressure. The residue was recrystallized from ethanol, yielding compound (6b)(30mg, 30%), m.p. 145–147°C. IR(KBr); υ=1685 cm^{-1}(C=O), 1580(C=N). ^1H NMR($CDCl_3$): δ=2.38(s, 3H, CH_3), 7.03(m, 2 aromatic H), 7.25(m, 6 aromatic H). MS(70 eV); m/z(%): 302(86)[M^+].

3-(m-Nitrophenyl)-4-(p-tolyl)-1,2,4-thiadiazole-5(4H) -one (6c)

Compound **(5c)** (200mg) was heated in diphenyl ether (0.5ml) in a tube for 10h at 175°C in the presence of a little amout of copper powder. After cooling, diethyl ether was added to the mixture and filtered. Diethyl ether was evaporated and the residue was first washed with petroleum ether (50–70°C), then recrytallized from ethanol to give compound (6c)(75mg, 37%), m.p. 143–145°C. IR(KBr), υ=1695cm^{-1}(C=O), 1618(C=N), 1529(NO_2). ^1H NMR($CDCl_3$): δ=2.39(s, 3H, CH_3), 7.07(m, 2 aromatic H), 7.25(m, 2 aromatic H), 7.48(m, 1 aromatic H), 7.64(m, 1 aromatic H), 8.24(m, 2 aromatic H). MS(70eV); m/z(%): 313(100)[M^+].

Acknowledgements
This work was supported by the Research Fund of Kocaeli University, project number: 16.

References

[1] H. Ağirbaş, D. Sümengen, Y. Dürüst and N. Dürüst, *Synth. Commun.*, **22(2),** 209–217 (1992).
[2] D. Sümengen and A. Pelter, *J. Chem. Soc. Perkin Trans. 1*, 687–691 (1983).
[3] Y. Dürüst, H. Ağirbaş and D. Sümengen, *Phosphorous, Sulfur and Silicon,* **62,** 47–51 (1991).
[4] H. Ağirbaş, Y. Dürüst and D. Sümengen, *Phosphorous, Sulfur and Silicon,* **66,** 321–324.(1992).
[5] H Ağirbaş, Y. Dürüst and A. Karahasanoğlu, *Phosporus, Sulfur and Silicon,* **114,** 173–178 (1996).
[6] H.R. Al-Kazimi, D.S. Tarbell, and D. Plant, *J. Am. Chem. Soc.,* **77,** 2479–2482 (1955).
[7] K. Miyazaki, *Tetrahedron Lett.,* 2793–2798 (1968).
[8] M.S. Newman and H.A. Karnes, *J. Org. Chem.,* **31,** 3980–3984 (1966).
[9] D.H. Powers and D.S. Tarbell, *J. Am. Chem. Soc.,* **78,** 70–71 (1956).
[10] B. Cross, R.J.G. Searle and R.E. Woodall, *J. Chem. Soc. (C),* 1833–1835 (1971).
[11] W.B. Ankers, C. Brown, R.F. Hudson, and A.J. Lawson, *J. Chem. Soc. Chem. Commun.,* 935–936 (1972).
[12] R.F. Hudson, A.J. Lawson and E.A.C. Lucken, *J. Chem. Soc. Chem. Commun.,* 807–808 (1971).
[13] R.F. Hudson, A.J. Lawson and K.A.F. Record, *J. Chem. Soc., Perkin Trans. 2,* 869–873 (1974).
[14] F. Gümüş, Y. Dürüst, N. Dürüst, and U. Abbasoğlu, *Pharmazie,* **48, H.11,** 868 (1993).
[15] R. Ün, and D. Sümengen, *Chim. Acta Turc.,* **4,** 131 (1976).
[16] G. d'Alo, M. Perghem, and P. Gruenanger, *Ann. Chim.,* **53(10),** 1405 (1963).