THE PHOSPHONOACETONITRILE-α-THIOAMIDES AS PRECURSORS OF PHOSPHONATED THIENOPYRIMIDINONES

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(Reçu le 16 Juillet 2013, accepté le 05 Septembre 2013)

ABSTRACT: Novel phosphonothienopyrimidinone derivatives were synthesized in four steps by using phenylisothiocyanate and active methylene compounds. The structures of the obtained compounds were confirmed by IR and NMR (^{1}H, ^{13}C, ^{31}P).

Keywords: Phosphonoacetonitrile-α-thioamides, Thiophenes, Phenylisothiocyanate, Ethylbromoacetate, Thienopyrimidinones.

RESUME: Nouvelles thienopyrimidinones phosphonatées ont été synthétisées en quatre étapes en partant de composés à méthylène activé et de phénylisothiocyanate. Les structures des composés obtenus ont été déterminées suite à une étude spectroscopique par IR et RMN (^{1}H,^{13}C, ^{31}P).

Mots clés: Phosphonoacétonitrile-α-thioamides, Thiophènes, Phénylisothiocyanate, Bromoacétate d'éthyle, Thiénopyrimidinones.

INTRODUCTION

The thienopyrimidine structure (a purine analogue) has recently received considerable attention. Indeed, many of its substituted derivatives, including thienotriazolopyrimidines [l], thienotetrazolopyrimidines [2], thienothiadiazolopyrimidine [3] and others, have pronounced antibacterial [4-7], antifungal [8], antiviral [9], anti-inflammatory [10, 1l] and herbicidal [12] activities. On the other hand, thienopyrimidines and their fused heterocyclic ring systems are potential bioactive molecules as they bear structural analogy and isoelectronic relations to purines [13]. A large number of fused thienopyrimidine derivatives exhibit biological activities as potential antimicrobial [14, 15], analgesic [16] and anticancer [17] agents.

Keeping in view of the above facts, we report here the synthesis of novel phosphono-thienopyrimidinone derivatives which might show enhanced biological activity due to the presence of the phosphonate group.

RESULTS AND DISCUSSION

The suggested synthetic plans to obtain the target compounds are shown in Schemes 1, 2 and 3. In Scheme 1, the starting diethoxyphosphorylacetonitrile **1** was prepared by phosphorylation of chloroacetonitrile according to the reported procedure [18]. The reaction of compound **1** with isothiocyanates performed in tetrahydrofuran as solvent, at room temperature, in the presence of an equimolar amount of potassium tert-butoxide, yielded the non-isolable potassium sulphide intermediate I. Treatment of the salt I with dilute hydrochloric acid furnished the corresponding phosphonoacetonitrile-α-thioamide derivative **2** in equilibrium with its tautomeric thiol form **2'**. The presence of the thiol form was verified by ^{1}H NMR spectral data which displayed a downfield singlet signal around 14 ppm due to the SH proton, besides the other expected signals. The ^{31}P

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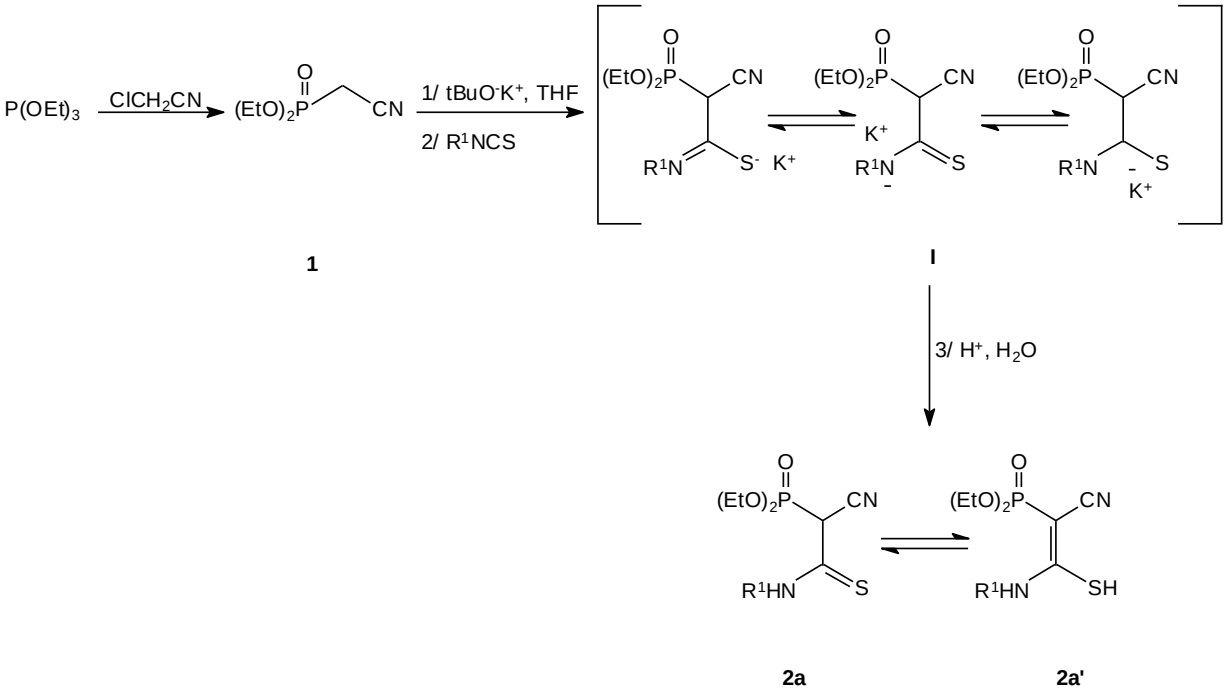
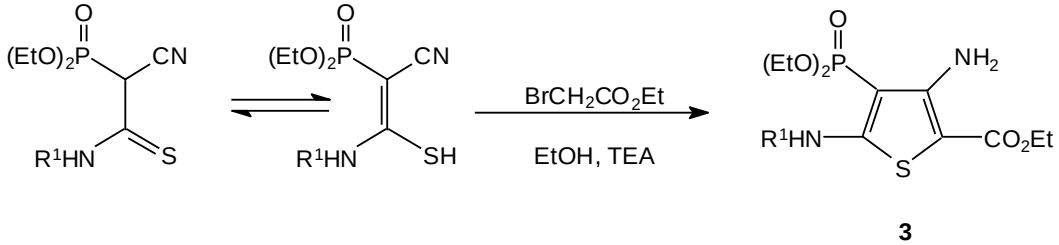
NMR spectra were characterized by tow signals around 10 and 14 ppm corresponding to the two tautomers.



2a,2a': R^1= Ph; **2b,2b':** R^1= p-ClPh; **2c,2c':** R^1= c-hexyl

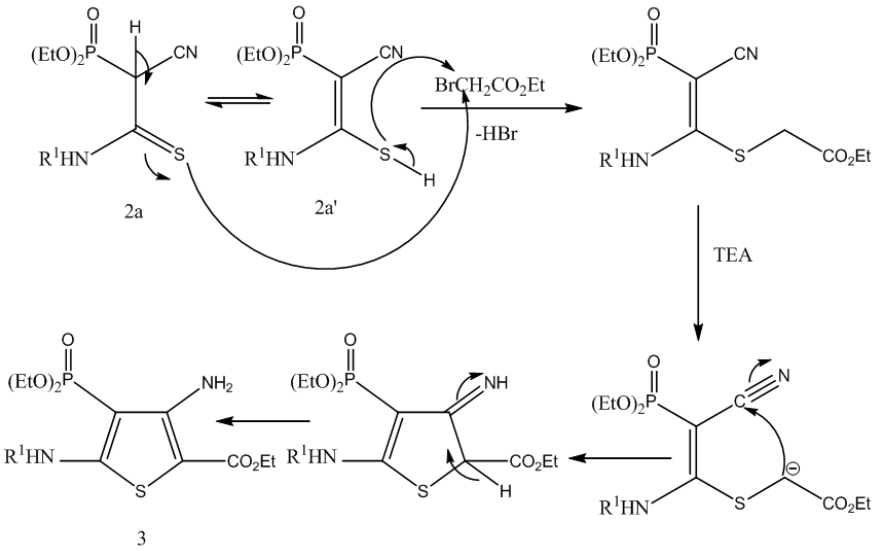
Scheme 1. Synthesis of compounds **2**.

The reaction of the latter products with α-halocarbonyl compounds, as a key step for the synthesis of polysubstituted thiophene derivatives was examined. Thus, compounds **2** reacted with ethyl bromoacetate, in refluxing ethanol, using a catalytic amount of triethylamine, to afford a single product identified as the phosphonoaminothiophene derivative **3** based on the spectral data of the isolated products. A plausible mechanism for the formation of the aminothiophenes **3** is given in scheme 2 and 3. The reaction is believed to begin with the alkylation of **2** with α-ethyl bromoacetate to form the non-isolable thioether which, in situ, underwent intramolecular cyclization via the nucleophilic addition of the active methylene group to the cyano function followed by a tautomerization, according to the Thorpee Ziegler reaction [19].



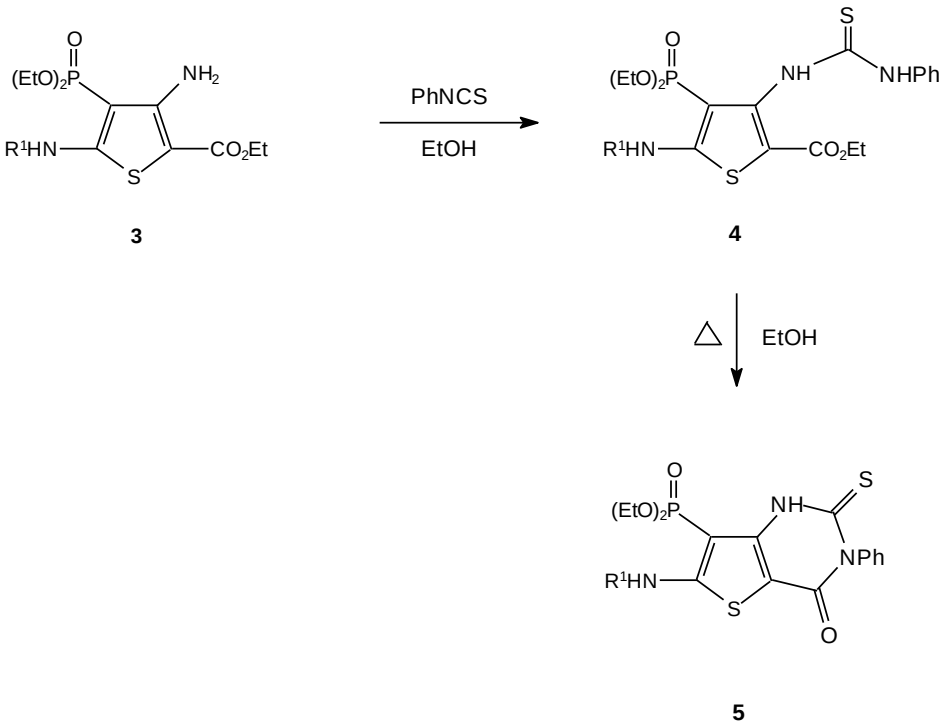
3a: R^1= Ph; **3b:** R^1= p-ClPh; **3c:** R^1= c-hexyl

Scheme 2. Synthesis of compounds **3**.



Scheme3. Proposed reaction mechanism for the formation of compounds **3**.

On the other hand, aminothiophene **3** was allowed to react with phenyl isothiocyanate in ethanol to afford the thiourea derivative **4**, which was heated with ethanol on a oil bath at 80 °C to afford the corresponding phosphonothienopyrimidinones **5**. Spectral data were in favor of these proposed thienopyrimidinone structures. The IR spectra of compounds **5** revealed the absence of NH_2 and CO_2Et absorption bands and the presence of new absorption bands at 1300 cm^{-1} assignable to the C=S group. The ^{13}C NMR spectra were characterized by signals around 179 and 188 ppm assignable respectively to the amide (C=O) and thiourea (C=S) functions. The ^{31}P NMR spectra showed a new singlet signal at 14 ppm corresponding to the phosphorus atom.



5a: R^1= Ph; **5b:** R^1= p-ClPh; **5c:** R^1= c-hexyl

Scheme 4. Synthesis of compounds **5**.

CONCLUSION

In conclusion, we successfully developed a four-step synthesis of novel phosphonothienopyrimidinone derivatives by using phenylisothiocyanate and active methylene compounds. The structures of the obtained compounds were confirmed by IR and NMR (^{1}H, ^{13}C, ^{31}P) spectroscopies.

EXPERIMENTAL

Melting points were determined on a Kofler bank. IR spectra were recorded from KBr on a Perkin-Elmer 197 spectrometer; only structurally significant bands are reported. NMR spectra were recorded on a Bruker-Spectrospin AC 300 spectrometer operating at 300 MHz for ^{1}H, 75.5 MHz for ^{13}C and 121 MHz for ^{31}P. Chemical shifts were measured relative to TMS in $CDCl_3$ as solvent. Materials: thin-layer chromatography (TLC): TLC plates (Merck, silica gel 60 F254 0.2 mm 200×200 nm); substances were detected using UV light at 254 nm.

Synthesis of aminodiethylphosphonothioacrylonitrile 2 and 2'

To a suspension of powdered tBuOK (1.3 mmol) in THF (20 mL) was added phosphonoacetonitrile (1mmol) and isothiocyanate (1mmol). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was poured into 10 mL of mixture of water and hydrochloric acid (80/20%). The combined organic layers were washed with water and dried with $MgSO_4$. After filtration, the solvent was evaporated in vacuo. The resultant solid products were collected and recrystallized from EtOH to give compounds **2**.

2a, 2a': Yield 70%; yellow powder; mp = 154°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm}: 1.20 (td, 6H); 4.20 (qd, 4H); 4.70 (d, 1H); 7.20-7.78 (m, H_{arom}); 10.80 (s, NH); 14.10 (s, SH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} :16.11-16.35 (CH_3); 49.42 (CH); 60.07 (-C=); 62.72-66,70 (CH_2); 112.73-119.56 (CN); 122.94-138.42 (C_{arom}); 170.17 (N-C-SH); 183.06 (N-C=S). ^{31}P NMR ($CDCl_3$, 121 MHz) δ_{ppm} : 10.49 (41.5%); 17.46 (58.5%). IR (KBr, ν cm^{-1}): NH=3438, SH=2542, CN=2234,P=O =1260.

2b, 2b': Yield 75%; yellow powder; mp = 128°C . ^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm} : 1.25 (td, 6H); 4.20 (qd, 4H); 4.80 (d, 1H); 7.10-7.68 (m, H_{arom}); 10.85 (s, NH); 13.95 (s, SH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} :16.26 (CH_3); 49.42 (CH); 61.01 (-C=); 63.42-67.07 (CH_2); 112.73-119.56 (CN); 123.80-137.02 (C_{arom}); 183.98 (N-C=S, N-C-SH);). ^{31}P NMR ($CDCl_3$, 121 MHz) δ_{ppm} : 10.10 (57.5%); 14.04 (42.5%). IR (KBr, ν cm^{-1}): NH=3431, SH=2532, CN=2236, P=O =1262.

2c, 2c': Yield 82%; yellow powder; mp = 136°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm} : 1.20 (td, 6H); 1.51-2.00 (m, $H_{c\text{-}hex}$); 4.20 (qd, 4H); 4.30 (d, 1H); 8.42 (s, NH); 14.20 (s, SH) . ^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} : 16.27 (CH_3); 24.29-47.86 ($C_{c\text{-}hex}$); 55.33 (-C=); 65.50-66.10 (CH_2); 112.87-112.87 (CN); 183.19 (N-C-SH); 183.26 (N-C=S). ^{31}P NMR ($CDCl_3$, 121 MHz) $\delta_{ppm:}$ 11.57 (89.5%); 14.27 (10.5%). IR (KBr, ν cm^{-1}): NH=3428, SH=2545, CN=2234, P=O =1259.

Synthesis of phosphonated aminothiophenes 3

To a solution of compound **2** (0.01 mol) in 20 mL ethanol, ethyl bromoacetate (0.01 mol) and few drops of triethylamine was added. The reaction mixture was refluxed for 5 h, and then allowed to cool. The formed solid product was collected, washed with ethanol and recrystallized from a mixture of EtOH/DMF (2:1) to afford the corresponding thiophene derivatives **3**.

3a: Yield 54% ; yellow powder; mp = 86°C . ^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm} : 1.21 (td, 6H) ; 1.45 (t, 3H); 4.10 (q, 2H) ; 4.20 (qd, 4H) ; 5.95 (s, NH_2); 7.20-7.38 (m, 5H $_{arom}$); 9.87(s, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} : 14.07 (CH_3); 16.11-16.35 (CH_3); 59.59 (CH_2) 60.90-62.88(CH_2); 116.41-140.40(C_{arom}); 124.16(P-C=); 163.77(P-C=C); 164.47(NH_2C=); 119.95 (=C-S); 167.66(CO_2). ^{31}P NMR ($CDCl_3$, 121 MHz) δ_{ppm} : 16.05. IR (KBr, ν cm^{-1}): NH_2 =3458, CO_2= 1720.

3b: Yield 62% ; yellow powder; mp = 80°C . ^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm} : 1.15 (td, 6H) ; 1.50 (t, 3H); 4.15 (q, 2H) ; 4.30 (qd, 4H) ; 6.05 (s, NH_2); 7.20-7.48 (m, 4H $_{arom}$); 8.87(s, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} : 13.95 (CH_3); 16.15-16.35 (CH_3); 60.59 (CH_2) 61.90-62.88(CH_2); 117.41-140.40(C_{arom});

126.16(P-C=); 162.77(P-C=C); 163.47(NH_2C=); 119.90 (=C-S); 168.66(CO_2). ^{31}P NMR ($CDCl_3$, 121 MHz) δ_{ppm}: 16.16. IR (KBr, ν cm^{-1}): NH_2 =3451, CO_2= 1725.

3c: Yield 65% ; yellow powder; mp = 90°C. ^1H NMR ($CDCl_3$, 300 MHz) δ_{ppm}: 1.20 (td, 6H) ; 1.51-2.00 (m, 11H $_{c\text{-}hex}$) ; 1.50 (t, 3H); 4.15 (q, 2H) ; 4.25 (qd, 4H) ; 5.80 (s, NH_2); 9.90(s, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm}: 14.95 (CH_3); 16.15-16.35 (CH_3); 60.59 (CH_2) 61.90-62.88(CH_2); 25.74-54.85($C_{C\text{-}hex}$); 127.16(P-C=); 164.77(P-C=C); 164.47(NH_2C=); 119.90 (=C-S); 168.66(CO_2). ^{31}P NMR ($CDCl_3$, 121 MHz) δ_{ppm}: 16.56. IR (KBr, ν cm^{-1}): NH_2 =3445, CO_2= 1730.

Synthesis of phosphonated thienopyrimidinones 5

A mixture of compound **3** (10 mmol) in 20 mL ethanol and phenyl isothiocyanate (10 mmol) for 2 h to afford thiourea **4**, which was heated with ethanol on a oil bath at 80 °C for 8 h. After cooling the solvent was removed under reduced pressure and the residue recrystallized from petrolium ether to give the product **5**.

5a: Yield 51% ; yellow powder; mp = 98 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ_{ppm}: 1.25(td, 6H); 4.20 (qd, 4H); 6.92(s, NH); 7.20-7.48 (m, 10H $_{arom}$); 8.87(s, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} :16.26-16.35 (CH_3); 62.33-62.39(CH_2); 68.73(P-C=C); 121.84-139.97(C_{arom}); 155.17(NHC=); 117.90 (=C-S); 179.84(CO); 188.60(C=S). ^{31}P NMR ($CDCl_3$, 121 MHz) δ_{ppm}: 14.71. IR (KBr, ν cm^{-1}): NH = 3350, C=O = 1670, C=S = 1350.

5b: Yield 52% ; yellow powder; mp = 91 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ_{ppm}: 1.15(td, 6H); 4.20 (qd, 4H); 5.92(s, NH); 7.20-7.48 (m, 9H $_{arom}$); 9.87(s, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} :16.28-16.38(CH_3); 62.33-62.39(CH_2); 68.43(P-C=C); 122.84-138.97(C_{arom}); 155.17(NHC=); 117.50 (=C-S); 178.84(CO); 187.61(C=S). ^{31}P NMR ($CDCl_3$, 121 MHz) δ_{ppm}: 14.51. IR (KBr, ν cm^{-1}): NH = 3320, C=O = 1675, C=S = 1350.

5c: Yield 55% ; yellow powder; mp = 88 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ_{ppm}: 1.25(td, 6H); 1.51-2.15 (m, 11H $_{c\text{-}hex}$); 4.20 (qd, 4H); 6.92(s, NH); 7.20-7.48 (m, 5H $_{arom}$); 8.87(s, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_{ppm} :16.26-16.35 (CH_3); 25.29-48.86($C_{c\text{-}hex}$); 62.33-62.39(CH_2); 68.73(P-C=C); 121.84-139.97(C_{arom}); 156,17(NHC=); 118.90 (=C-S); 177.84(CO); 188.60(C=S). ^{31}P NMR ($CDCl_3$, 121 MHz) δ_{ppm}: 14.81. IR (KBr, ν cm^{-1}): NH = 3150, C=O = 1675, C=S = 1300.

REFERENCES

[1] Shishoo, Devani MB, Ullas CV, Ananthan S, Bhadti VS, *J. Heterocycl. Chem.* **1981**,*18*,43-46.
[2] Shishoo CI, Devani MB, Marvekar MD rr, *I. J. Chem*, **1982,** *21B*, 666-668.
[3] Russo F, Santagati M, Caruso A, Trombadore S, Amico-Roxas M, *Eur. J. Med. Chem*, **1986**, *21*,119-122
[4] Roth B, *US Pat*, **1969**, 3 470 183; Chem Abstr, **1970**, *72*, 21706m
[5] Rasowsty A, Chaykwsky M, Chen KN, Lin M, Modest El, *J. Med. Chem.*, **1973** *16*,185-188
[6] El-Kerdawy MM, Yousif MY, El-Emam AA, Moustafa MA, El-Sherbeny MA, *Chim. Pharm. J.*, **1993**, *45*.457-163.
[7] Devani MB, Shishoo CJ, Pathak US, Sharma BG, G&hale SV, Padhyda AC, *Indian J. Chem.*, **1977**, *16B*, 575-578.
[8] Ram VI, Pandey HN, Marsha L, *Arch. Pharm.*, **1979**, *312*,586-590.
[9] Samsonova NV, Kharizomenova LA, Givenv AN, Kaplina EK, *Kim Pt. wrm. Zh*, **1981**, *15*,40-45; *Chem. Abstr*, **1982**, *96*,68930.
[10] Vega S, Alonso J, Diaz JA, *Eur. J. Med. Chem.*, **1991**, *26*, 323-329
[11] Santilli AA, Kim DH, *US Pat*, **1972**, 3, 644, 351; *Chem. Abstr*,**1972,** *76*, 140878.
[12] Ram VJ, Pandey HK, Vlientinck AJ, *J. Heterocycl. Chem.*,**1981**, *18*, 1277-1280.
[13] Y.A. Ibrahim, A.H.M. Elwahy, *Adv. Heterocycl. Chem.* **1996**, *65*, 235-281.
[14] M.H. Bhuiyan, K.M. Rahman, K.H. Abdur Rahim, M.I. Hossain, M. Abu Naser, *Acta Pharm*. **2006**,*56*, 441-450.
[15] M.I. Hegab, N.A. Hassan, A.E. Rashad, A.A. Fahmy, F.M.E. Abdel-Megeid, *Phosphorus Sulfur Silicon Relat. Elem.* **2007**, *182*, 1535-1556.
[16] V. Alagarsamy, S. Meena, K.V. Ramseshu, V.R. Solomon, K. Thirumurugan, K. Dhanabal, M. Murugan, *Eur. J. Med. Chem.* **2006**, *41*, 1293-1300.
[17] S.I. Alqasoumi, F.A. Ragab, A.M. Alafeefy, M. Galal, M.M. Ghorab, *Phosphorus Sulfur Silicon Relat. Elem.* **2009**, *184*, 3241-3257.
[18] B. A. Arbusov et coll ; Isv. Akad. Nauk. Otdel. *Khim. Nauk.* **1959**, 41, *Chem. Abstr.* **1959**, 53, 15035.
[19] S.A. Ryndina, A.V. Kadushkin, N.P. Soloveva, V.G. Granik, *Russ. Chem. Bull*. **2002**, 51, 854-859.