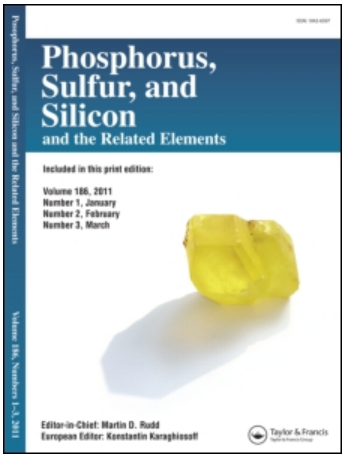


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Studies on Phosphonium Ylides-XXIII: The Behavior of Active and Stabilized Phosphonium Ylides Towards Thiohydantoins

Leila S. Boulos[a]; El-Sayed M. A. Yakout[a]; Mona H. N. Arsanious[a]
[a] National Research Centre, Dokki, Cairo, Egypt

To cite this Article Boulos, Leila S. , Yakout, El-Sayed M. A. and Arsanious, Mona H. N.(2006) 'Studies on Phosphonium Ylides-XXIII: The Behavior of Active and Stabilized Phosphonium Ylides Towards Thiohydantoins', Phosphorus, Sulfur, and Silicon and the Related Elements, 181: 7, 1615 — 1623
To link to this Article: DOI: 10.1080/10426500500366517
URL: http://dx.doi.org/10.1080/10426500500366517

Phosphorus, Sulfur, and Silicon, 181:1615–1623, 2006

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500500366517

Taylor & Francis
Taylor & Francis Group

Studies on Phosphonium Ylides-XXIII: The Behavior of Active and Stabilized Phosphonium Ylides Towards Thiohydantoins

Leila S. Boulos
El-Sayed M. A. Yakout
Mona H. N. Arsanious
National Research Centre, Dokki, Cairo, Egypt

*Thiohydantoin **1** reacts with 2-oxovinylidenetriphenylphosphorane (**2**) to give 1-methyl-2-thioxo-6-(triphenyl-λ^5-phosphoranylidene)-hexahydro-furo[2,3-d]imidazol-5-one (**5**). On the other hand, when **1** reacts with phosphorus ylides **3a–d**, the respective olefinic adducts **6a**, **6b**, **8**, and the dimeric product **7** were obtained together with triphenyl-phosphine oxide. Moreover, the application of reagent **4** on **1** renders the new product 4-methyl-2,3-diphenyl-2,3,4,6-tetrahydro-1-oxa-1,3,4,6-tetra-azapentalene-5-thione. Mechanisms accounting for the formation of the products are presented based on analytical and spectroscopic data.*

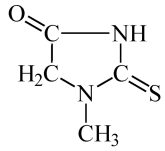
Keywords 2-oxovinylidenetriphenylphosphorane; phosphonium ylides; phosphoranylidene adduct; tetraaza-pentalene; thiohydantoin

Hydantoins and thiohydantoins are traditionally being considered as useful intermediates in peptide synthesis and structural determination.[1] Several derivatives of parent heterocycles display significant biological activities and are being employed either as established drugs in clinical practice (anticonvulsants, anti-epileptics)[2] or as fungicides or herbicides in agriculture.[3]

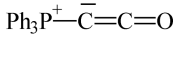
This together with our interest in organophosphorus chemistry[4–8] enhanced the synthesis of new phosphorus compounds incorporating such important nuclei that may possibly lead to further biological activity. The present study deals with the reaction of the active phosphacumulene ylide, namely 2-oxovinylidenetriphenylphosphorane (**2**) with 1-methyl-2-thiohydantoin (**1**), and compares the reactivity of the active phosphacumulene ylide (**2**) with the reactivity of stabilized

Received March 28, 2005; accepted August 29, 2005.
Address correspondence to Leila S. Boulos, National Research Centre, El-Tahrir St., Dokki, Cairo, 12622, Egypt. E-mail: leilasadek@hotmail.com

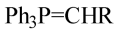
phosphonium ylides (**3a–d**) and iminophosphorane (**4**) toward the previously mentioned thiohydantoin (**1**) (Scheme 1).



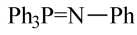
1



2



3



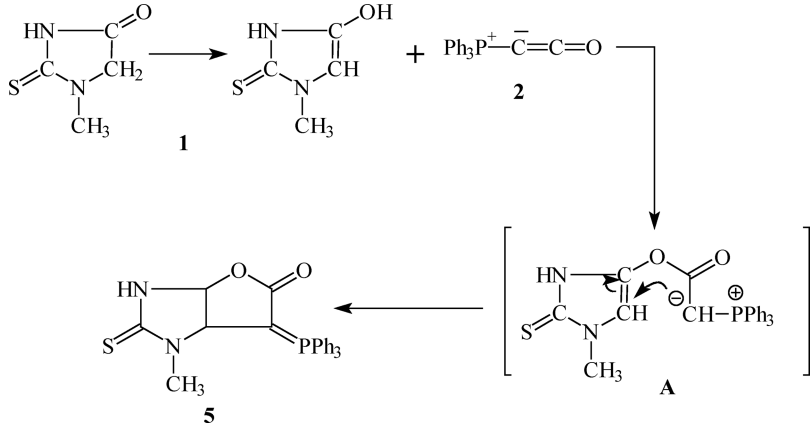
4

3a, R = $COOC_2H_5$
3b, R = $COOCH_3$
3c, R = $COOC(CH_3)_3$
3d, R = CHO

SCHEME 1

RESULTS AND DISCUSSION

We have found that 1-methyl-2-thiohydantoin (**1**) reacts with the mole equivalent of 2-oxovinylidenetriphenylphosphorane (**2**), in dry tetrahydrofuran, at r.t. for 9 h to give a yellow crystalline product assigned structure (**5**). Structural support for 1-methyl-2-thioxo-6-(triphenyl-λ^5-phosphoranylidene)-hexahydro-furo[2,3-d]imidazol-5-one was based upon correct elemental and spectroscopic data (Scheme 2).



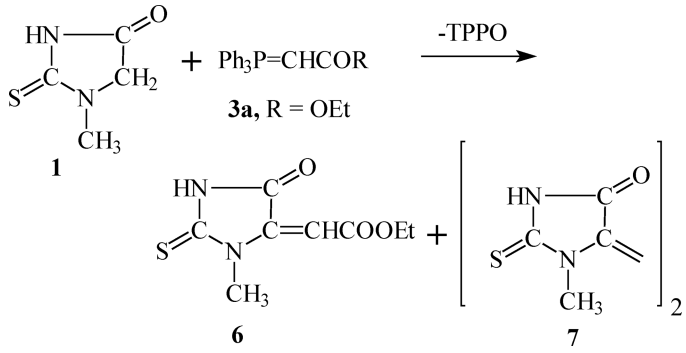
SCHEME 2

The IR spectrum of compound **5** revealed the presence of strong absorption bands at 3420 cm^{-1} (NH), 1740 (C=O, lactone),[9] 1620 (C=P),[10] and 1440 (p-aryl).[11] The P NMR of compound **5** (in $CDCl_3$) showed signals at 3.11 ppm (s, 3H, N–CH_3), 3.37 (d, 1H, CH=C), 4.91(d, 1H, CH–O–CO), and 7.53–7.64 (m, 15H, aromatics) and a broad signal at 2.3 ppm (1H, NH, exchangeable with D_2O). In the ^{13}C NMR spectrum of compound **5**, it showed signals at 185.6 ppm (C=S), 163.4 (C=O), P–Ph_3 (128.62, 128.42, 128.2, 128.3), 132.45 (C=P, $J_{CP} = 161.6$ Hz), 86.4 (CH–O–CO), 39.45 (N–CH_3), and 37.7 (CH–C). A signal at +22.68 ppm was observed in the ^{31}PNMR spectrum of **5**, which supports structure **5** and fits with phosphorane.[12] The mass spectrum of compound **5** yielded a prominent ion peak at m/e 432, which is in accord with structure **5**.

The reaction of active phosphacumulene ylide **2** with 1-methyl-2-thiohydnatoin (**1**) occurs through the acylation of the ylide on the carbon atom to give the intermediate (**A**), which cyclized through the migration of the α-proton to the electron-rich center of the molecule to give the cyclic phosphoranylidene derivative **5** (Scheme 2).[13]

We have also investigated the reactivity of 1-methyl-2-thiohydantoin **1** toward stable phosphonium ylides (**3a–d**) to determine the preferential site of attack.

When 1-methyl-2-thiohydantoin **1** was treated with one equivalent of ethoxycarbonylmethylenetriphenylphosphorane (**3a**) in refluxing benzene, compounds **6**, **7**, and triphenylphosphine oxide were isolated in good yields (Scheme 3).



SCHEME 3

It is worth mentioning that when we repeated the previously discussed experiment in an inert atmosphere (N_2 atmosphere), the same reaction products **6**, **7**, and triphenylphosphine oxide was isolated (Scheme 3).

The structure elucidation of (1-methyl-4-oxo-2-thioxo-imidazolidin-5-ylidene)-acetic acid ethylester **6a** is based on the following evidence: The elemental analysis and molecular weight determination (MS) of **6a** support the molecular formula $C_8H_{10}N_2O_3S$ (214.24); accordingly, MS: m/z = 214 (M^+, 100% base peak). The main features of the IR spectrum of **6a** (in KBr) were the presence of both the carbonyl and thiocarbonyl absorption bands appearing in the spectrum of **1** at 1733 cm^{-1} (C=O, amide), and 1174 cm^{-1} (C=S), respectively, and at 3231 cm^{-1} (NH). Moreover, the IR spectrum of **6a** reveals the presence of an absorption band at 1760 cm^{-1} (C=O, ester) assigned for the ester carbonyl band. The ^1H NMR (in $CDCl_3$) of compound **6a** disclosed the presence of signals at 1.30 ppm (t, 3H, $COOCH_2\ \underline{CH_3}$), 3.11 (s, 1H, $N{-}CH_3$), 4.25 (q, 2H, $COO\underline{CH_2}CH_3$), and at 6.15 (s, 1H, $=\underline{CH}COO$ Et). The ^{13}CNMR spectrum of compound **6a** reveal the presence of signals at $\delta = 187.58$ ppm (C=S, thioamide), 166.91 (C=O, amide), 164.5 (C=O, ester), 143.1 ($\underline{C}$=CHCOOEt), 97.15 (C=$\underline{C}$HCOOEt), 61.27 ($COO\underline{C}H_2CH_3$), 28.79 ($N{-}\underline{C}H_3$), and at 14.10 ($CO_2CH_2\underline{C}H_3$).

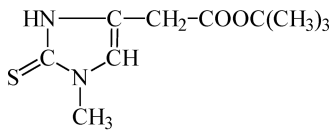
The structural elucidation of the dimeric compound 1,1′-dimethyl-2-dithio-[5,5′]biimidazolidinylidene-4,4′-dione (**7**) has been determined on the basis of IR, ^1H NMR, MS, and elemental analysis (cf. Experimental section) (Scheme 3).

The reaction sequence could be assumed to take place via an active methylene nucleophilic attack at the ylidic carbon, liberating the phosphorus as triphenylphosphine oxide and the exocyclic olefinic linkage containing compound **6** (possibly due to the presence of unavoidable moisture and/or an oxygen-sensitive intermediate).

Similarly, the reaction of thiohydantoin **1** with methoxycarbonylmethylenetriphenylphosphorane **3b** proceeds in refluxing benzene under a N_2 atmosphere to give compounds **6b** (60% yield) and **7** (20% yield). Triphenylphosphine oxide has also been isolated from the reaction mixture. Structural assignments for compounds **6b** and **7** are based upon elemental and mass spectral analyses, IR, and ^1H NMR (cf. Experimental section).

We have found that 1-methyl-2-thioxoimidazolidin-4-one (**1**) reacts with an equimolar amount of tert-butoxycarbonylmethylentriphenylphosphorane (**3c**) to give the new product 1-methyl-2-thioxo-2,3-dihydro-1H-imidazol-4-yl-acetic acid tert-butyl ester (**8**) in a 65% yieled and the dimeric structure **7** in a 15% yield. Triphenylphosphine oxide was also isolated and identified from the reaction medium. The structure of the olefinic compound **8** is indicated by its analysis, ^1H, and ^{13}C NMR, and mass spectral data (cf. Experimental section).

The reaction of **1** with formylmethylene-triphenylphosphorane (**3d**) has also been investigated. The treatment of **1** with mol equivalents of **3d** in refluxing toluene leads to the formation of the dimeric compound **7**



8

SCHEME 4

as the sole reaction product. Triphenylphosphine oxide was also isolated and identified (Scheme 4).

We have also investigated the reaction of 1-methyl-2-thioxoimidazolidin-4-one (**1**) with N-phenyliminophosphorane (**4**) to establish whether or not it would behave in a similar manner. We have found that thiohydnatoin (**1**) reacts with two mol equivalents of N-phenyl-iminophosphorane **4** to give the new adduct 4-methyl-2,3-diphenyl-2,3,4,6- tetrahydro-1-oxa-2,3,4,6-tetraaza-pentalene-5-thione (**9**) (Scheme 5). Triphenylphosphine was also isolated from the reaction medium and identified. The structure of the new product **9** was inferred from its correct analytical values and the IR spectrum, which lacks an absorption band in the carbonyl region.

The mass spectrum of compound (**9**) showed the ion peak at m/z = 310 [M^+, 100%]. A possible explanation for the formation of product **9** is illustrated in Scheme 5. Thiohydantoin **1** reacts with two mole equivalents of phosphinimine **4** to give the new product 4-methyl-2,3-diphenyl-2,3,4,6-tetrahydro-1-oxa-2,3,4,6-tetraazapentalene-5-thione (**9**) through a loss of triphenylphosphine followed by the subsequent dehydrogenation accompained with a loss of H_2 (autoxidation).

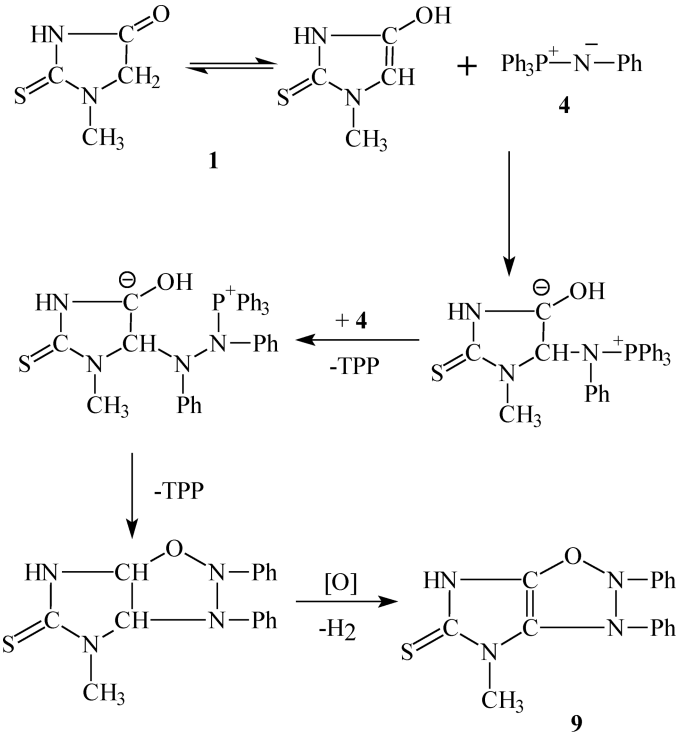
Based on the results of the present investigation, it could be inferred that the active and stabilized phosphonium ylides behave differently toward 1-methlyl-2-thioxo-imidazolidin-4-one (**1**).

While the reaction of the active phophacumulene ylide **2** with thiohydantoin (**1**) resulted in the formation of the cyclic 1-methyl-2-thioxo-6-(triphenyl-λ^5-phosphoranylidene)-hexahydro-furo[2,3-d]-imidazol-5-one (**5**), a different behavior was observed in the reaction of **1** with stabilized ylides (**3a–d**) and the iminophosphorane **4**, depending on the stability of reaction products.

Also, these findings represent an anomalous behavior of the Wittig reagents.

EXPERIMENTAL

All melting points are uncorrected and were taken on an electrothermal 9100 apparatus. The IR spectra were recorded on a Perkin Elmer Infrared Spectrophotometer model 157 (Grating) using KBr. The ^{13}C, ^{1}H,



SCHEME 5

and ^{31}P NMR spectra were obtained on Jeol GLMEX 270 MHz instrument (super conducting magnet) in $CDCl_3$ or DMSO-d_6 using tetramethylsilane as an internal standard. The mass spectra were obtained with Finnigan MAT-SSQ 7000 spectrophotometer (70 eV). Microanalyses were performed by the Central Services Laboratory at National Research Centre Dokkai, Cairo, Egypt.

1-methylthiohydantoin easily can be prepared by boiling 1-methylhydantoin with phosphorus pentasulfide in acetonitrile for 1 h m.p. and mixed m.p.[14]

1-Methyl-2-thioxo-6-(triphenyl-λ^5-phosphornylidene)-hexahydro-furo[2,3-d]imidazol-5-one (5)

To a solution of 1-methyl-2-thiohydantoin (**1**) (0.001 mol, 0.13 g) in dry tetrahydrofuran (25 mL), 2-oxovinylidene-triphenylphosphorane (**2**) (0.001 mole, 0.302 g) was added. The reaction mixture was stirred at r.t. for 9 h (the reaction was TLC controlled); then the volatile

materials were evaporated. The residue was washed several times with hot pet. ether, and the residual substance was recrystalized from chloroform to give compound **5** as yellowish brown crystals m.p. 179–181°C, yield 78%. Anal. calcd. for $C_{24}H_{21}N_2O_2PS$ (432.48): C, 66.65; H, 4.89; N, 6.48; P, 7.16; S, 7.41. Found: C, 66.15; H, 4.98; N, 6.08; P, 6.92; S, 7.21%. IR (cm^{-1}): 3420 (NH), 1740 (C=O, lacton), 1620 (C=P), 1440 (P-Phenyl). ^1H NMR, $CDCl_3$: δ3.11 ppm (s, 3H, N—CH_3); 3.37 (d, 1H, CH=C); 4.91 (d, 1H, CH—O—CO); 7.53–7.64 (m, 15H, aromatics); 2.30 (bs, 1H, NH, exchangeable with D_2O). ^{13}CNMR, $CDCl_3$: 185.6 ppm (C=S); 163.4 (C=O); 128.62, 128.42, 128.20, 128.30 (aromatic carbons); 132.45 (C=P, $J_{CP} = 161.6$ Hz); 86.4 (CH—O—CO); 39.45 (N—CH_3); 37.7 (CH—C). ^{31}P NMR, $\delta = +22.68$ ppm. MS: m/z 432 (M^+, 100%).

Reactions of 1-Methyl-2-thiohydantoin (1) with Phosphonium Ylides 3a–d

General Procedure

1-methyl-2-thiohydatoin (**1**) (0.001 mole, 0.13 g) and carboxymethylenetriphenylphosphoranes **3a–d** (0.001 mol) were refluxed in dry benzene (25 mL) for about 10 h. (The reactions were TLC controlled.) After the reactions were finished, the volatile materials were evaporated on a little amount of silica gel; then the mixture was separated on silica gel column chromatography using an eluant mixture of ethyl acetate/n-hexane 10:90%. It was found that the first fraction obtained from the column were the products **6a**,**b** and **8** in the case of Wittig reagents **3a**,**b**,**c**, respectively; the second fraction was triphenylphosphine (TPPO); the third fraction was the dimeric compound **7** in all the reactions.

Ethyl-2-(3-Methyl-5-oxo-2-thioxoimidazolidin-4-ylidene) Acetate (6a)

Red needles crystals, m.p. 142–144°C, yield 65%. Anal. calcd. for $C_8H_{10}N_2O_3S$ (214.24): C, 44.85; H, 4.70; N, 13.08; S, 14.97. Found: C, 44.52; H, 4.37; N, 12.81; S, 14.63%. IR (cm^{-1}): ν 3231 (NH), 1760 (C=O, ester), 1733 (C=O, amide), 1174 (C=S, thioamide). ^1H NMR, $CDCl_3$: δ 1.30 ppm (t, 3H, $COOCH_2C\underline{H}_3$), 3.11 (s, 1H, N—CH_3), 4.25 (q, 2H, $COOC\underline{H}_2CH_3$), 6.15 (s, 1H, =$C\underline{H}COOC_2H_5$) and. . . (1H, NH, exchangeable with D_2O). ^{13}C NMR, $CDCl_3$: δ 187.58 ppm (C=S, thioamide), 166.9 (C=O, amide), 164.5 (C=O, ester), 143.1 ($\underline{C}$=$CHCOOC_2H_5$), 97.15 (C=$\underline{C}HCOOC_2H_5$), 61.27 ($COO\underline{C}H_2CH_3$), 28.79 (N—CH_3), and 14.10 ($COOCH_2\underline{C}H_3$). MS: m/z = 214 (M^+-, 100%).

Methyl-2-(3-Methyl-5-oxo-2-thioxoimidazolidin-4-ylidene)-acetate (6b)

Orange needles crystals, m.p. 205–207°C, yield 62%. Anal. calcd. for $C_7H_8N_2O_3S$ (200.22): C, 41.99; H, 4.03; N, 13.99; S, 16.02. Found: C, 41.75; H, 3.69; N, 13.65; S, 15.80%. IR (cm^{-1}): ν 3306 (NH), 1771 (C=O, ester), 1733 (C=O, amide), 1162 (C=S, thioamide). ^{1}HNMR, $CDCl_3$: δ3.35 ppm (s, 1H, N—CH_3), 3.80 (s, 3H, —CO—OCH_3), 6.20 (s, 1H, =CH—$COOCH_3$); 9.35 (s, 1H, NH, exchangeable with D_2O). MS: m/z = 200 (M^+, 90%).

3,3′-Dimethyl-2,2′-dithioxo-[4,4′]biimidazol-idinylidene-5,5-dione (7)

Brown crystals, m.p. >300°C, yield ~20%. Anal. calcd. for $C_8H_8N_4O_2S_2$ (256.31): C, 37.49; H, 3.15; N, 21.86; S, 25.02. Found: C, 37.23; H, 2.94; N, 21.48; S, 24.64%. IR (cm^{-1}): ν3232 (NH), 1731 (C=O, amide), 1136 (C=S, thioamide). ^{1}H NMR, DMSO-d_6: δ3.38 ppm (s, 6H, 2 N—CH_3), 8 (s, 2H, 2 NH, exchangeable with D_2O). MS: m/z = 256 (M^+, 100%).

(1-Methyl-2-thioxo-2,3-dihydro-1H-imidazol-4-Yl)-acetic Acid Tert-butyl ester (8)

Yellowish crystals, m.p. 170–172°C, yield 75%. Anal. calcd. for $C_{10}H_{16}N_2O_2S$ (228.31): C, 52.61; H, 7.06; N, 12.27; S, 14.04. Found: C, 52.28; H, 6.77; N, 12.01; S, 13.69%. IR (cm^{-1}): ν 3145 (NH), 1750 (C=O, ester), 1166 (C=S, thioamide). ^{1}H NMR, $CDCl_3$: δ1.35 ppm (s, 9H, 3 CH_3), 4.0 (s, 3H, N—CH_3), 7.15 (s, 1H, ethylenic H), 2.0 (s, 1H, NH, exchangeable with D_2O). ^{13}C NMR, $CDCl_3$: δ29.0 ppm (3 CH_3), 39.8 (N—CH_3), 46.0 (CH_2, aliphatic), 73.3 (—C—, ter); 108.9, 125.7 (C=C, ring); 171.01 (C=O, ester), 178.2 (C=S). MS: m/z = 228 (M^+, 100%).

4-Methyl-2,3-diphenyl-2,3,4,6-tetrahydro-1-oxa-2,3,4,6-tetraazo-pentalene-5-thione (9)

To a solution of 1-methyl-2-thiohydation (**1**) (0.001 mol, 0.13 g) in dry toluene (25 mL) as a solvent, N-phenyliminophosphorane (4) (0.002 mol, 0.706 g) was added, and the reaction mixture was refluxed for 8 h. Then, the solvent was evaporated, and the residue was separated on column chromatography packed with silica gel; the eluent system was acetone/pet. ether (b.p. 60–80°C) with percent of 10:90. The first fraction was triphenylphosphin m.p. and mixed m.p. 79–81°C, and the second fraction was 4-methyl-2,3-diphenyl-2,3,4,6-tetrahydro-1-oxa-2,3,4,6-tetraaza-pentalene-5-thione (**9**) as a yellow crystals, m.p.

198–200°C, yield 62%. Anal. calcd. for $C_{16}H_{14}N_4OS$ (310.37): C, 61.92; H, 4.55; N, 18.05; S, 10.33. Found: C, 61.71; H, 4.19; N, 17.69; S, 10.05%. IR (cm^{-1}): ν 3220 (NH), the disappearance of the band of C=O, amide, 1145 (C=S, thioamide). ^1H NMR, DMSO-d_6: δ 3.30 ppm (s, 3H, N–CH_3), 6.9–7.45 ppm (m, 10H, aromatics); 8.6 (s, NH, exchangeable with D_2O). MS: m/z = 310 (M^+, 100%).

REFERENCES

[1] M. Bodansky, In *Principles of Peptide Synthesis*, p. 35–45 (Springer-Verlag, Berlin, 1993).
[2] C. A. Lopez and G. G. Trigo, *Adv. Heterocycl. Chem*., **38,** 224 (1985) and references cited therein.
[3] J. Marton, J. Enisz, S. Hosztafi, and T. Timar, *J. Agric. Food Chem*., **41,** 148 (1993).
[4] L. S. Boulos and H.A. Abd El-Malek, *Heteroatom Chem*., **10,** 263 (1999).
[5] L. S. Boulos and M. H. N. Arsanious, *Hetroatom*, **10,** 337 (1999).
[6] L. S. Boulos and M. H. N. Arsanious, *Heteroatom*, **12,** 511 (2001).
[7] L. S. Boulos and M. H. N. Arsanious, *Synthetic Communication*, **32,** 2779 (2002).
[8] L. S. Boulos and H. A. Abd El-Malek, *Phosphorus, Sulfur, and Silicon*, **179,** 97 (2004).
[9] L. J. Bellamy, *The Infrared Spectra of Complex Molecules* (Wiley & Sons, New York, 1964).
[10] F. Ramirez, O. P. Madan, and C. P. Smith, *J. Org. Chem*., **30,** 2284 (1965).
[11] D. H. Williams and I. Fleming, *Spectroscopic Methods in Organic Chemistry*, p. 55–69 (McGraw-Hill, Maidenhead, Berkshire, UK, 1987).
[12] H. J. Bestmann, *Angew. Chem*., **89,** 361 (1977).
[13] H. J. Bestmann, G. Schmid, and D. Sandmeier, *Angew. Chem*., **88,** 92 (1976); *Angew. Chem. Int. Ed. Engl*., **15,** 115 (1976).
[14] W. Marckwal, M. Neumak, and R. Stelzner, *Chem. Ber*., **24,** 3278 (1891).