

Study of Reaction between Activated Acetylenes and *N,N'*-Diethyl-2-thiobarbituric Acid in the Presence of Isocyanides or Triphenylphosphine

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ABSTRACT: In a series of separate experiments reaction between *N,N'*-diethyl-2-thiobarbituric acid and acetylenic diesters in the presence of isocyanides or triphenylphosphine led to highly functionalized 4*H*-pyrano[2,3-*d*]thiopyrimidine or 1,4-di-ionic organophosphorus derivatives. The ¹H NMR spectra of diethyl-7-(2,6-dimethylphenylamino)-4-oxo-2-thio-1,3-diethyl-4*H*-pyrano[2,3-*d*]pyrimidine-5,6-dicarboxylate showed dynamic NMR effect that was attributed to restricted rotation around the aryl-nitrogen single bond. Activation free energy ($\Delta G^\ddagger$) for this process is about $54.85 \pm 2 \text{ kJ mol}^{-1}$. Betaines as 1,4-diionic organophosphorus compounds in this reaction are possessed of two vicinal stereogenic centers and exist in the solution as a mixture of two diastereoisomers. © 2010 Wiley Periodicals, Inc. *Heteroatom Chem* 21:228–235, 2010; Published online in

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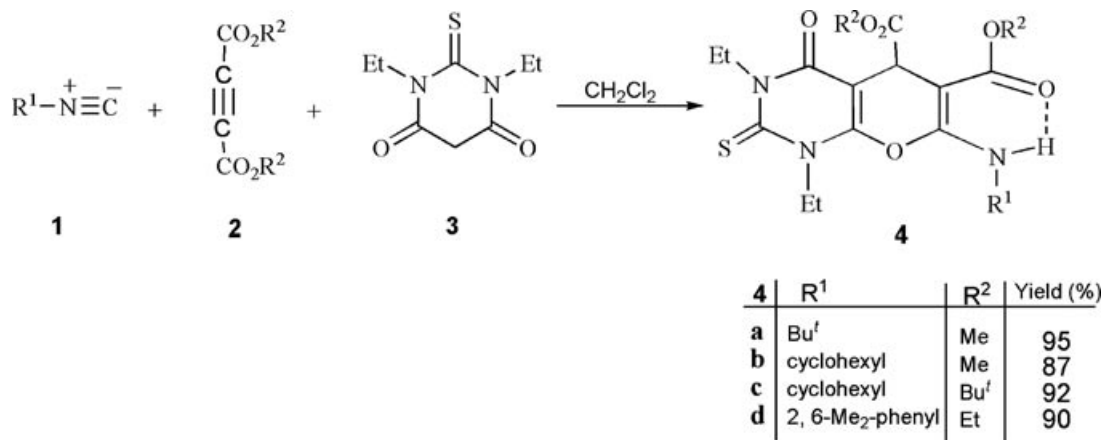
INTRODUCTION

In recent years, the synthetic application of multifunctional heterocycles has been widely investigated [1,2]. In spite of extensive developments in the chemistry of modified isocyanates [3], little attention has been paid to the synthesis of pyrimidine [4–7]. In general, barbiturates and thiobarbiturates are drugs from pyrimidine derivatives. Today these compounds are infrequently used as anticonvulsants and also induction of anesthesia [8]. Barbiturate drugs are used as sedative-hypnotic agents [9]. In addition, recently, there has been increasing interest in the synthesis of organophosphorus compounds, that is those bearing a carbon atom bond directly to a phosphorus atom [10–31]. This interest arises from the greater stability of these compounds compared to the phosphate analogues [32] and recognition of the value of such compounds in a wide range

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SCHEME 1

of industrial, biological, and chemical synthetic aspects [33,34].

In the set of investigations made on the development of heterocyclic and organophosphorus compound synthesis [35–40], we now describe a one-pot, synthesis of *N,N'*-diethyl-2-thiobarbituric acid containing heterocyclic **4** and organophosphorus derivatives **9** using isocyanides **1** or triphenylphosphine **7** and acetylenic diesters **2** in the presence of *N,N'*-diethyl-2-thiobarbituric acid **3** (see Schemes 1 and 4).

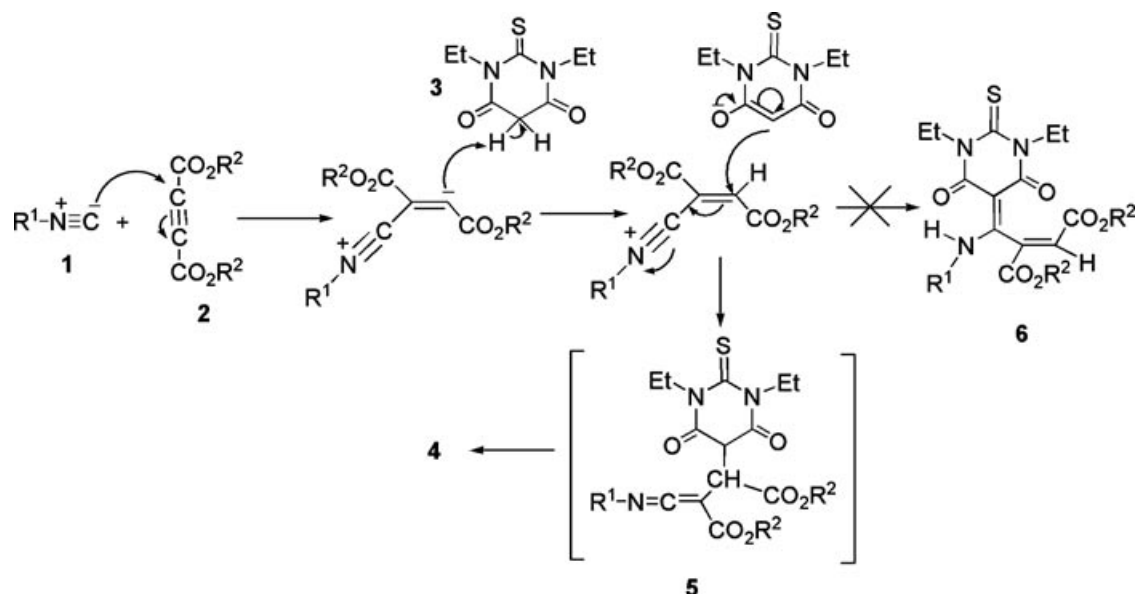
RESULTS AND DISCUSSION

The reaction between alkyl or aryl isocyanides **1** and electron-deficient acetylenic esters **2** in the presence of strong CH-acid **3** proceeded at ambient temperature in CH₂Cl₂ and was completed within 5 days. The structure of **4** was assigned on the basis of elemental analyses, infrared (IR), ¹H, ¹³C NMR, and mass spectral data. The mass spectra of 4*H*-pyrano[2,3-*d*]thiopyrimidines **4a–d** are similar and displayed molecular ion peaks at appropriate *m/z* values. Initial fragmentations involve loss of the side chains and scission of the enaminoester system. The ¹H NMR spectrum of compound **4a** exhibited nine single sharp lines, readily recognizable arising from C-methyl ($\delta = 1.26$ and 1.40), *tert*-butyl ($\delta = 1.44$), methoxy ($\delta = 3.68$ and 3.71), methylene ($\delta = 4.50$ and 4.57), methine ($\delta = 4.58$), and a broad band for the NH group at $\delta = 8.99$ ppm, indicating intramolecular hydrogen bond formation with the vicinal carbonyl group.

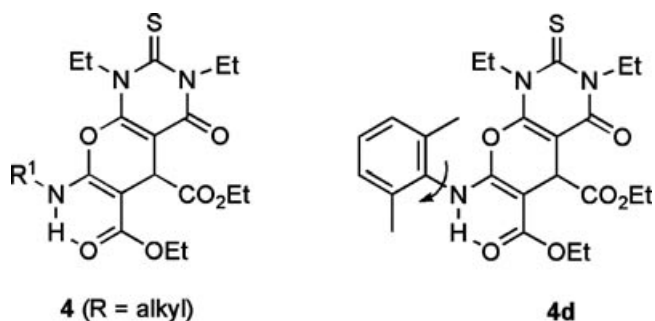
The ¹³C NMR spectrum showed 17 distinct resonances consistent with the enaminoester structure. The structural assignments of compounds **4a–d** made on the basis of NMR spectra were supported

by their IR spectra. Of special interest are the strong carbonyl absorption bands at 1683–1717 cm^{−1} and fairly broad NH peak at about 3165–3335 cm^{−1} for all compounds. (See the Experimental section). Although we have not yet established the mechanism of the reaction between alkyl or aryl isocyanides and dimethyl acetylenedicarboxylate (DMAD) in the presence of *N,N'*-diethyl-2-thiobarbituric acid in an experimental manner, a possible explanation is proposed in Scheme 2. On the basis of the well-established chemistry of isocyanides [10–13,41,42], it is reasonable to assume that compound **4** results from initial addition of the alkyl isocyanide **1** to the acetylenic ester **2** and subsequent protonation of the 1:1 adduct by *N,N'*-diethyl-2-thiobarbituric acid **3** (Scheme 2). Then the positively charged ion is probably attacked by the enolate anion of the CH acid in accord with two ways. The first step (Scheme 2) involves a *Michael* addition that leads to the keteneimine **5**. Compound **5** apparently isomerizes under the reaction condition, to produce the fused heterocyclic system **4**. Enaminocarbonyl compound **6** is unfavored according to the second way (Scheme 2) because spectral data were not compatible with the structure of compound **6**.

The presence of two separate signals for the Ar-Me₂ groups in both ¹H and ¹³C NMR spectra of **4d** can be explained on the basis of restricted rotation around the *N*-aryl bond (see Scheme 3). The ¹H NMR spectrum of **4d** in 1,2-dichlorobenzene at 70°C showed resonances arising from C-Me protons, which are appreciably broadened in comparison with corresponding signals in the spectrum measured at room temperature, whereas the *N*-Et and O-Et resonances remain unchanged. The Ar-Me₂ protons coalesce near 90°C and appear as a fairly sharp symmetrical resonance at 110°C. No further



SCHEME 2



SCHEME 3

dynamic NMR effect was observed up to 120°C, as the highest temperature investigated.

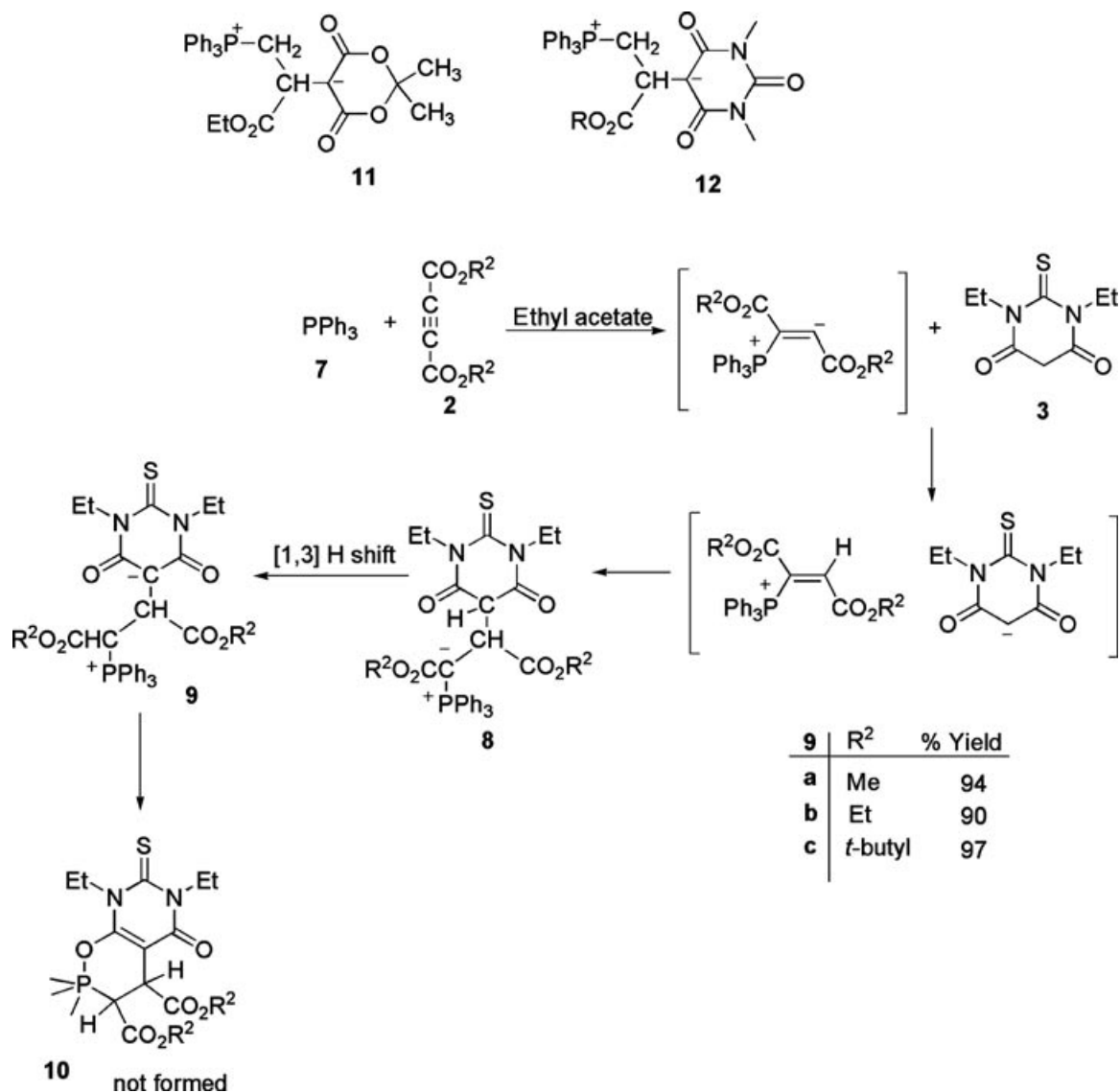
Although no extensive line-shape analysis was undertaken for **4d**, nevertheless the variable temperature spectra allowed calculating the free energy barrier for the restricted *N*-aryl bond rotation [43] in **4d**. From the coalescence of the *N*-Me proton resonances and using the expression $k = \pi \Delta\nu/\sqrt{2}$, the first-order rate constant (k) was calculated for the *N*-aryl bond rotation in **4d** about 66.81 s⁻¹ at 90°C

(see Table 1). An application of the absolute rate theory with a transmission coefficient of 1 gave free energy of activation ($\Delta G^\ddagger$) of 54.85 kJ mol⁻¹, in which all known sources of errors were estimated and included [44]. The experimental data available were not suitable for obtaining meaningful values of $\Delta H^\ddagger$ and $\Delta S^\ddagger$, even though the errors in $\Delta G^\ddagger$ were not large [45].

In a series of other experiment from reactions between triphenylphosphine and acetylenic diesters in the presence of *N,N'*-diethyl-2-thiobarbituric acid, the hitherto unknown butanedioates **9a–c** generated in 90–97% yield (Scheme 4). All the compounds are stable crystalline solids whose structure is fully supported by elemental analyses and IR, ¹H, ¹³C, and ³¹P NMR spectroscopy and mass spectroscopy data. The mass spectra of these 1:1:1 adducts displayed fairly weak molecular ion peaks. Any initial fragmentation involved the loss of ester moieties and scission of the ring. A cyclic six-membered ring structure for compound **9** (compound **10**) is unfavored because spectral data were not compatible with the structure of compound **10**.

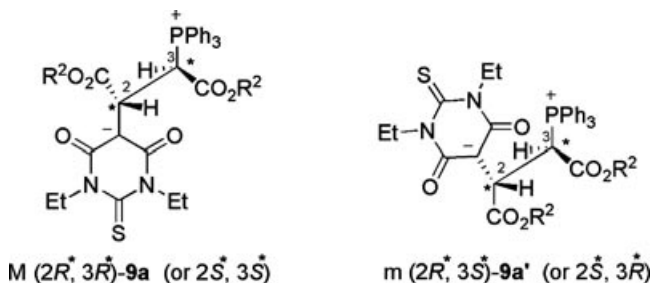
TABLE 1 First-Order Rate Constants, Standard *Gibbs* Energies, and Selected Activation Parameters for **4d** in 1,2-Dichlorobenzene

Compound	<i>T</i> (°C)	<i>Ar-Me</i> (δ , ppm)		$\Delta\nu$ (Hz)	<i>K</i> (s ⁻¹)	<i>T</i> _c (°K)	$\Delta G^\ddagger$ (kJ mol ⁻¹)
4a	27	2.27	2.37	30	66.81	263	54.85 ± 2
	110		2.35				



SCHEME 4

If the compound **10** was obtained instead of compound **9**, then we were to expect a doublet at about $\delta = 160$ for the C—O—P moiety in the ^{13}C NMR spectra. Structure **9** was further confirmed by the



SCHEME 5

^{31}P NMR spectroscopic data ($\delta = 23\text{--}25$), which is in agreement with the presence of a $\text{Ph}_3\text{P}^+-\text{C}$ grouping [24,25]. On the basis of the chemistry of trivalent phosphorus nucleophiles [1–5], it is reasonable to assume that compound **9** results from the initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the 1:1 adduct by CH-acid **5**. Then, the positively charged ion is attacked by the enolate anion the CH-acid to generate ylide **8**. Compound **8** apparently isomerizes, under the reaction conditions, to produce the 1,4-dionic compound **9**.

The ^1H NMR (500 MHz) spectra of compounds **9a–c** displayed signals for vicinal methine protons at δ 4.81–5.91, which appear as two sets of double doublets for the major and minor diastereoisomers. The vicinal proton–proton coupling constant

($^3J_{\text{HH}}$) as a function of a torsion angle can be obtained from the Karplus equation [25]. Typically, J_{gauche} and J_{anti} vary between 1.5–5 and 10–14 Hz, respectively. Observation of $^3J_{\text{HH}}$ 10.2–12.1 Hz for the vicinal protons in major and minor diastereoisomers of compounds **9a–c** indicates an antiarrangement for these protons. The assignments of the (2*S*,3*S*)-**9** and (2*R*,3*S*)-**9** configurations of **9a–c** are based on the three-bond carbon–phosphorus coupling, $^3J_{\text{PC}}$. Vicinal carbon–phosphorus coupling depends on configuration, as expected, trans couplings being larger than cis ones. The Karplus relation can be derived from the data for organophosphorus compounds with tetra- and penta-valent phosphorus [41]. The observation of $^3J_{\text{PC}}$ of 11–15 Hz for the C(CO)₂ group is in agreement with the (2*R**,3*R**)-**9** for the major diastereoisomer (see the Experimental section). On the other hand, the measurement of $^3J_{\text{PC}}$ of 18–20 Hz for the ester C=O group is in accord with the (2*R**,3*S**)-**9** for the minor diastereoisomer (see Scheme 5). In conclusion, we have found that the reaction of 1,3-diethyl-2-thiobarbituric acid, with dialkyl acetylenedicarboxylates in the presence of triphenylphosphine, leads to a facile synthesis of highly functionalized 1,4-diionic organophosphorus compounds **9a–c** with excellent yields.

In fact, the reaction of isocyanides or triphenylphosphine with electron-deficient acetylenic diesters in the presence of *N,N'*-diethyl-2-thiobarbituric acid provides a simple one-pot entry into the synthesis of polyfunctional 4*H*-pyrano[2,3-*d*]thiopyrimidine or highly functionalized 1,4-diionic organophosphorus compounds of potential synthetic interest. The ^1H NMR spectra of the product **4d** displayed the dynamic NMR effect that is attributed to restricted rotation around the aryl-nitrogen single bond and polarized carbon–carbon double bond.

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses for C, H, and N were performed using a Heraeus (Banau, Germany) CHN-O-Rapid analyzer. IR, ^1H , ^{13}C , and ^{31}P NMR spectra were measured on a Shimadzu (Tokyo, Japan) IR-460 and Bruker (Rheinstetten, Germany) DRX-500 Avance spectrometer at 500.1, 125.8, and 202.4 MHz, respectively. Mass spectra were recorded on a Shimadzu GC/MS QP 1100 EX mass spectrometer, operating at an ionization potential of 70 eV. Isocyanides, alkyl acetylenedicarboxylates, and *N,N'*-diethyl-2-thiobarbituric acid were obtained from Fluka and used without further purification.

The process for the preparation of *dimethyl-7-tert-butylamino-4-oxo-2-thio-1,3-diethyl-4H-pyrano[2,3-*d*]pyrimidine-5,6-dicarboxylate* (**4a**) is described as an example. To a magnetically stirred solution of *N,N'*-diethyl-2-thiobarbituric acid (0.20 g, 1 mmol) and DMAD (0.14 g, 1 mmol) in CH_2Cl_2 (6 mL), dropwise a mixture of *tert*-butyl isocyanide (0.83 g, 1 mmol) in CH_2Cl_2 (2 mL) was added at -10°C over 10 min. The reaction mixture was then allowed to warm up to room temperature and to stand for 5 days. The solvent was removed under reduced pressure, the solid residue was washed by (2×3) cm^3 cold diethyl ether, and the product **4a** was obtained as white powder. Yield: 0.36 g (85%), mp = 148–149°C, IR (KBr) (ν_{max} , cm^{-1}): 3190 (N–H); 1685, 1738 (C=O). ^1H NMR (500.1 MHz, CDCl_3): δ_{H} 1.26 (3H, t, $J = 7.0$ Hz, NCH_2CH_3), 1.40 (3H, t, $J = 7.0$ Hz, NCH_2CH_3), 1.44 (9H, s, CMe_3), 3.68 and 3.71 (6H, s, 2 OCH_3), 4.50 and 4.57 (4H, m, 2 NCH_2CH_3), 4.58 (1H, s, CH), 8.99 (1H, br s, $\text{NH}\cdots\text{O}=\text{C}$). ^{13}C NMR (125.8 MHz, CDCl_3): δ_{C} 11.31 and 12.90 (2 OCH_2CH_3), 30.40 (NCMe_3), 35.60 (CH), 43.84 and 44.67 (2 NCH_2CH_3), 52.83 (CMe_3), 51.44 and 52.57 (2 OCH_3), 74.21 and 92.99 (2 $\text{C}=\text{C}-\text{O}$), 151.41 (C=S), 158.94 and 159.07 (2 $\text{C}=\text{C}-\text{O}$), 169.27 (NCO), 173.56 and 174.98 (2 C=O). MS (m/z , %): 425 (M^+ , 1), 336 (66), 310 (59), 223 (63), 195 (20), 178 (20), 163 (26), 57 (100), 41 (65). Anal Calcd for $\text{C}_{19}\text{H}_{27}\text{N}_3\text{O}_6\text{S}$ (425.50): C, 53.63; H, 6.40; N, 9.88; Found: C, 53.85; H, 6.41; N, 9.75.

*Dimethyl-7-cyclohexylamino-4-oxo-2-thio-1,3-diethyl-4H-pyrano[2,3-*d*]pyrimidine-5,6-dicarboxylate* (**4b**)

White Powder. Yield: 0.40 g (83%), mp = 152–153°C, IR (KBr) (ν_{max} , cm^{-1}): 3314 (N–H); 1691, 1730 (C=O). ^1H NMR (500.1 MHz, CDCl_3): δ_{H} 1.18–2.10 (10H, m, 5 CH_2), 1.27 (3H, t, $J = 6.8$ Hz, NCH_2CH_3), 1.41 (3H, t, $J = 6.8$ Hz, NCH_2CH_3), 3.58–3.80 (1H, m, NCH), 3.70 and 3.72 (6H, 2s, 2 $\text{O}-\text{CH}_3$), 4.32–4.60 (4H, m, 2 NCH_2CH_3), 4.58 (1H, s, CH), 8.62 and 8.64 (1H, d, $\text{NH}\cdots\text{O}=\text{C}$). ^{13}C NMR (125.8 MHz, CDCl_3): δ_{C} 11.36 and 12.75 (2 NCH_2CH_3), 24.47, 25.18, 33.69, 33.95, and 35.67 (5 CH_2 of cyclohexyl), 35.70 (CH), 43.81 and 44.94 (2 NCH_2CH_3), 51.12 (N–CH), 51.33 and 52.63 (2 OCH_3), 72.77 and 92.92 (2 $\text{C}=\text{C}-\text{O}$), 151.43 (C=S), 157.59 and 159.08 (2 $\text{C}=\text{C}-\text{O}$), 169.05 (NCO), 173.60, 175.08 (2 C=O). MS (m/z , %): 451 (M^+ , 2), 392 (100), 305 (23), 223 (38), 163 (29), 59 (36), 55 (95), 41 (61). Anal Calcd for $\text{C}_{21}\text{H}_{29}\text{N}_3\text{O}_6\text{S}$ (451.53): C, 55.86; H, 6.47; N, 9.31; Found: C, 56.07; H, 6.38; N, 9.25.

Di-tert-Butyl-7-cyclohexylamino-4-oxo-2-thio-1,3-diethyl-4H-pyrano[2,3-d]pyrimidine-5,6-dicarboxylate (4c)

Pale-Yellow Powder. Yield: 0.39 g (78%), mp = 124–127°C, IR (KBr) ($\nu_{\max}$, cm^{-1}): 3300 (N–H); 1686, 1717 (C=O). ^1H NMR (500.1 MHz, CDCl_3): δ_{H} 1.26–1.85 (10H, m, 5 CH_2), 1.28 (3H, t, J = 6.8 Hz, NCH_2CH_3), 1.37 (3H, t, J = 6.8 Hz, NCH_2CH_3), 1.46 and 1.51 (18H, 2s, 2 CMe_3), 3.54 (1H, m, N–CH), 4.45 (1H, s, CH), 4.56 and 4.60 (4H, m, 2 NCH_2CH_3), 8.58 (1H, s, $\text{NH}\cdots\text{O}=\text{C}$). ^{13}C NMR (125.8 MHz, CDCl_3): δ_{C} 11.41 and 12.73 (2 NCH_2CH_3), 24.75 and 25.26 (2 CH_2 of cyclohexyl), 28.00 and 28.48 (6 Me of 2 CMe_3), 27.80, 33.90, and 34.15 (3 CH_2 of cyclohexyl), 37.25 (CH), 43.72 and 44.90 (2 NCH_2CH_3), 51.21 (N–CH), 80.27 and 81.25 (2 CMe_3), 74.45 and 93.71 (2 C=C–O), 151.55 (C=S), 157.33 and 159.05 (2C=C–O), 168.35 (NCO), 172.90 and 175.06 (2C=O). MS (m/z , %): 535 (M^+ , 5), 434 (28), 378 (100), 379 (33), 252 (28), 57 (33). Anal Calcd for $\text{C}_{27}\text{H}_{41}\text{N}_3\text{O}_6\text{S}$ (535.70): C, 60.54; H, 7.71; N, 7.84; Found: C, 60.65; H, 7.60; N, 7.81.

Diethyl-7-(2,6-dimethylphenylamino)-4-oxo-2-thio-1,3-diethyl-4H-pyrano[2,3-d]pyrimidine-5,6-dicarboxylate (4d)

Pale-Yellow Powder. Yield: 0.43 g (87%), mp = 182–185°C, IR (KBr) ($\nu_{\max}$, cm^{-1}): 3245 (N–H); 1693, 1734 (C=O). ^1H NMR (500.1 MHz, CDCl_3): δ_{H} 0.73 (3H, t, J = 6.5 Hz, $\text{N}-\text{CH}_2\text{CH}_3$), 1.25 (3H, t, J = 6.5 Hz, $\text{N}-\text{CH}_2\text{CH}_3$), 1.23–1.42 (6H, m, 2 OCH_2CH_3), 2.24 and 2.35 (6H, 2s, ArMe_2), 3.90–4.24 (4H, m, 2 OCH_2CH_3), 4.25–4.52 (4H, m, $\text{N}-\text{CH}_2\text{CH}_3$), 4.68 (1H, s, CH), 7.10–7.21 (3H, m, ArH), 7.28 (1H, s, $\text{NH}\cdots\text{O}=\text{C}$). ^{13}C NMR (125.8 MHz, CDCl_3): δ_{C} 11.34 and 11.95 (2 NCH_2CH_3), 14.16 and 14.35 (2 OCH_2CH_3), 18.25 and 18.36 (ArMe_2), 36.06 (CH), 43.70 and 44.87 (2 NCH_2CH_3), 60.38 and 61.41 (2 OCH_2CH_3), 74.81 and 92.78 (2C=C–O), 128.03, 128.19, 128.37, 133.78, 136.04, and 137.04 (6 C_{arom}), 151.48 (C=S), 157.19 and 159.04 (2 C=C–O), 168.67 (NCO), 172.95 and 174.95 (2C=O). MS (m/z , %): 501 (M^+ , 10), 428 (100), 241 (26), 156 (20), 144 (21), 105 (17), 77 (12). Anal Calcd for $\text{C}_{25}\text{H}_{31}\text{N}_3\text{O}_6\text{S}$ (501.60): C, 59.86; H, 6.23; N, 8.38; Found: C, 59.91; H, 6.20; N, 8.42.

Preparation of (2R,3R*)-1,3-Diethyl-4,6-dioxo-2-thioxo-5-[2-(triphenylphosphonio)-1,2-bis(methoxycarbonyl)ethyl]tetrahydropyrimidin-5-ide (9a)*

General Procedure. To a magnetically stirred solution of triphenylphosphine (0.26 g, 1 mmol) and

1,3-diethyl-2-thiobarbituric acid (0.2 g, 1 mmol) in ethyl acetate (5 mL), dropwise a mixture of dimethyl acetylene-dicarboxylate (0.14 g or 1 mmol) in ethyl acetate (2 mL) over 4 min was added. After 40 min stirring at room temperature, the product was filtered and washed with cold diethyl ether (3 $\times$ 5 mL) to give a cream powder. Yield 0.57 g, 94%. mp 160–162°C; IR (KBr) ($\nu_{\max}$, cm^{-1}): 1734, 1741, and 1749 (C=O). MS (m/z , %): 604 (M^+ , 3), 546 ($\text{M}-2\text{Et}$, 42), 486 ($\text{M}-2\text{CO}_2\text{Me}$, 37), 406 ($\text{M}-\text{C}_8\text{H}_{10}\text{N}_2\text{O}_2\text{S}$, 27), 262 (Ph_3P , 81), 183 (Ph_2P , 100), 108 (PhP , 42), 77 (Ph , 29). Anal. Calcd. for $\text{C}_{32}\text{H}_{33}\text{O}_6\text{N}_2\text{SP}$ (604.65): C, 63.56; H, 5.50; N, 4.63. Found: C, 63.61; H, 5.57; N, 4.60.

Major isomer. ^1H NMR (500.1 MHz, CDCl_3): δ 1.29 (6H, t, $^3J_{\text{HH}}$ = 6.9 Hz, 2 NCH_2CH_3), 3.18, 3.30 (6H, 2s, 2 OCH_3), 4.56 (4H, m, 2 ABX_3 system 2 NCH_2CH_3), 5.02 (1H, dd, $^3J_{\text{HH}}$ = 10.5 Hz and $^3J_{\text{PH}}$ = 6.6 Hz, P–CH–CH), 5.80 (1H, dd, $^3J_{\text{HH}}$ = 10.5 Hz and $^2J_{\text{PH}}$ = 14.5 Hz, P–CH–CH), 7.53–7.87 (15H, m, 3 C_6H_5); ^{13}C NMR (125.8 MHz, CDCl_3): δ 12.78 (2 NCH_2CH_3), 41.55 and 41.60 (2 NCH_2), 42.54 (d, $^2J_{\text{PC}}$ = 4.7 Hz, P–CH–CH), 43.33 (d, $^1J_{\text{PC}}$ = 41.6 Hz, P–CH), 52.71 and 52.93 (2 OCH_3), 87.71 (d, $^3J_{\text{PC}}$ = 11.2 Hz, P–C–C–C), 120.76 (d, $^1J_{\text{PC}}$ = 88.0 Hz, C_{ipso}), 129.54 (d, $^3J_{\text{PC}}$ = 12.9 Hz, C_{meta}), 134.12 (C_{para}), 134.28 (d, $^2J_{\text{PC}}$ = 9.5 Hz, C_{ortho}), 161.14 ($\text{O}=\text{C}-\text{C}=\text{O}$), 166.88 and 173.74 (2C=O, ester), 176.09 (C=S). ^{31}P NMR (202.4 MHz, CDCl_3): δ 24.28 ((Ph) $_3\text{P}^+-\text{C}$).

Minor isomer. ^1H NMR (500.1 MHz, CDCl_3): δ 1.17 (6H, t, $^3J_{\text{HH}}$ = 6.9 Hz, 2 NCH_2CH_3), 3.31, 3.59 (6H, 2s, 2 OCH_3), 4.20 (4H, m, 2 ABX_3 system 2 NCH_2CH_3), 5.09 (1H, dd, $^3J_{\text{HH}}$ = 11.3 Hz and $^3J_{\text{PH}}$ = 7.0 Hz, P–CH–CH), 5.84 (1H, dd, $^3J_{\text{HH}}$ = 11.3 Hz and $^2J_{\text{PH}}$ = 15.2 Hz, P–CH–CH), 7.53–7.87 (15 H_{aro} , m, 3 C_6H_5); ^{13}C NMR (125.8 MHz, CDCl_3): δ 12.78 (2 NCH_2CH_3), 42.01 and 42.18 (2 NCH_2), 42.46 (P–CH–CH), 43.18 (d, $^1J_{\text{PC}}$ = 50.8 Hz, P–CH), 52.55 and 52.71 (2 OCH_3), 87.99 (d, $^3J_{\text{PC}}$ = 2.5 Hz, P–C–C–C), 120.78 (d, $^1J_{\text{PC}}$ = 86.3 Hz, C_{ipso}), 129.51 (d, $^3J_{\text{PC}}$ = 12.9 Hz, C_{meta}), 134.08 (C_{para}), 134.28 (d, $^2J_{\text{PC}}$ = 9.5 Hz, C_{ortho}), 161.03 ($\text{O}=\text{C}-\text{C}=\text{O}$), 167.33 (d, $^2J_{\text{PC}}$ = 1.7 Hz, C=O, ester), 173.17 (d, $^3J_{\text{PC}}$ = 18.0 Hz, C=O, ester), 175.69 (C=S). ^{31}P NMR (202.4 MHz, CDCl_3): δ 23.97 ((Ph) $_3\text{P}^+-\text{C}$).

(2R,3R*)-1,3-Diethyl-4,6-dioxo-2-thioxo-5-[2-(triphenylphosphonio)-1,2-bis(ethoxycarbonyl)ethyl]tetrahydropyrimidin-5-ide (9b)*

White Powder. Yield: 0.57 g, 90%. mp = 162–164°C; IR (KBr) ($\nu_{\max}$, cm^{-1}): 1728, 1735, and 1746 (C=O). MS (m/z , %): 632 (M^+ , 5), 574 ($\text{M}-2\text{Et}$, 23), 486 ($\text{M}-2\text{CO}_2\text{Et}$, 36), 449 ($\text{M}-\text{PPh}_2$, 49), 262 (PPh_3 , 100), 262 (PPh_2 , 96), 183 (PPh , 52), 77 (Ph , 28). Anal.

Calcd. for $C_{34}H_{37}O_6N_2SP$ (632.71): C, 64.54; H, 5.89; N, 4.43. Found: C, 64.69; H, 6.04; N, 4.51.

Major isomer. 1H NMR (500.1 MHz, $CDCl_3$): δ 0.87–1.32 (12H, m, $2OCH_2CH_3$ and $2NCH_2CH_3$), 3.61 and 3.78 (4H, 2m, 2ABX₃ system, $2OCH_2CH_3$), 4.61 (4H, m, ABX₃ system $2NCH_2CH_3$), 5.29 (1H, br, P–CH–CH), 5.66 (1H, br, P–CH–CH), 7.48–7.90 (15H, m, $3C_6H_5$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 12.72 ($2NCH_2CH_3$), 13.56 and 13.79 ($2OCH_2CH_3$), 41.60 and 41.66 ($2NCH_2$), 42.58 (d, $^2J_{PC} = 4.5$ Hz, P–CH–CH), 43.38 (d, $^1J_{PC} = 43.3$ Hz, P–CH), 61.81 and 62.62 ($2OCH_2CH_3$), 88.52 (d, $^3J_{PC} = 12.0$ Hz, P–C–C–C), 121.32 (d, $^1J_{PC} = 88.3$ Hz, C_{ipso}), 129.50 (d, $^3J_{PC} = 12.9$ Hz, C_{meta}), 133.87 (d, $^4J_{PC} = 2.6$ Hz, C_{para}), 134.35 (d, $^2J_{PC} = 9.7$ Hz, C_{ortho}), 161.00 ($O=C-C-C=O$), 166.88 and 173.74 ($C=O$, ester), 176.05 ($C=S$). ^{31}P NMR (202.4 MHz, $CDCl_3$): δ 24.28 ((Ph)₃P⁺–C).

Minor isomer. 1H NMR (500.1 MHz, $CDCl_3$): δ 0.87–1.32 (12H, m, $2OCH_2CH_3$ and $2NCH_2CH_3$), 3.61 and 3.78 (4H, 2m, 2ABX₃ system, $2OCH_2CH_3$), 4.21 (4H, m, ABX₃ system, $2NCH_2CH_3$), 5.07 (1H, dd, $^3J_{HH} = 11.0$ Hz and $^3J_{PH} = 6.0$ Hz, P–CH–CH), 5.90 (1H, dd, $^3J_{HH} = 11.0$ Hz and $^3J_{PH} = 13.2$ Hz, P–CH–CH), 7.48–7.90 (15H, m, $3C_6H_5$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.31 ($2NCH_2CH_3$), 14.05 and 14.19 ($2OCH_2CH_3$), 41.91 and 41.98 ($2NCH_2$), 42.49 (d, $^2J_{PC} = 4.6$ Hz, P–CH–CH), 42.66 (d, $^1J_{PC} = 50.3$ Hz, P–CH), 61.33 and 62.23 ($2OCH_2CH_3$), 88.67 (d, $^3J_{PC} = 2.3$ Hz, P–C–C–C), 118.02 (d, $^1J_{PC} = 86.3$ Hz, C_{ipso}), 129.45 (d, $^3J_{PC} = 12.9$ Hz, C_{meta}), 133.87 (d, $^4J_{PC} = 2.6$ Hz, C_{para}), 134.28 (d, $^2J_{PC} = 9.2$ Hz, C_{ortho}), 161.00 ($O=C-C-C=O$), 166.64 (d, $^2J_{PC} = 1.6$ Hz, $C=O$, ester), 172.60 (d, $^3J_{PC} = 18.0$ Hz, $C=O$, ester), 175.66 ($C=S$). ^{31}P NMR (202.4 MHz, $CDCl_3$): δ 23.94 ((Ph)₃P⁺–C).

(2R*,3R*)-1,3-Diethyl-4,6-dioxo-2-thioxo-5-[2-(triphenylphosphonio)-1,2-bis(tert-butoxy-carbonyl)ethyl]tetrahydropyrimidin-5-ide (9c)

White Powder. Yield: 0.67 g, 97%. mp = 176–178°C; IR (KBr) (ν_{max} , cm^{-1}): 1724, 1732, and 1743 ($C=O$). MS (m/z , %): 688 (M^+ , 4), 615 ($M-OCMe_3$, 34), 587 ($M-CO_2CMe_3$, 29), 490 ($M-C_8H_{10}N_2O_2S$, 46), 262 (PPh_3 , 100), 183 (PPh_2 , 82), 108 (PPh , 36), 77 (Ph , 27). Anal. Calcd. for $C_{38}H_{45}O_6N_2SP$ (688.81): C, 66.26; H, 6.58; N, 4.07. Found: C, 66.32; H, 6.61; N, 3.95.

Major isomer. 1H NMR (500.1 MHz, $CDCl_3$): δ 0.94 and 0.99 (18H, 2s, $2CMe_3$), 1.07–1.23 (6H, br, $2NCH_2CH_3$), 4.56 (4H, br, $2NCH_2CH_3$), 4.85 (1H, dd, $^3J_{HH} = 10.4$ Hz, $^3J_{PH} = 6.2$ Hz, P–CH–CH), 5.64 (1H, dd, $^3J_{HH} = 10.4$ Hz, $^2J_{PH} = 13.9$ Hz, P–CH–CH), 7.43–7.85 (15H, m, $3C_6H_5$); ^{13}C NMR (125.8 MHz, $CDCl_3$):

δ 12.70 ($2NCH_2CH_3$), 27.05 and 27.36 (2s, $2CMe_3$), 41.31 and 42.17 ($2NCH_2$), 42.42 (d, $^2J_{PC} = 4.7$ Hz, P–CH–CH), 43.45 (d, $^1J_{PC} = 42.9$ Hz, P–CH), 81.63 and 84.01 (2C, $2OCMe_3$), 88.36 (d, $^3J_{PC} = 11.9$ Hz, P–C–C–C), 122.23 (d, $^1J_{PC} = 88.9$ Hz, C_{ipso}), 129.26 (d, $^3J_{PC} = 12.8$ Hz, C_{meta}), 133.43 (C_{para}), 134.41 (d, $^2J_{PC} = 9.6$ Hz, C_{ortho}), 160.99 ($O=C-C-C=O$), 165.52 and 172.76 (2 $C=O$, ester), 175.75 ($C=S$). ^{31}P NMR (202.4 MHz, $CDCl_3$): δ 25.17 ((Ph)₃P⁺–C).

Minor isomer. 1H NMR (500.1 MHz, $CDCl_3$): δ 1.02 and 1.27 (18H, 2s, $2CMe_3$), 1.07–1.23 (6H, br, $2NCH_2CH_3$), 4.18 (4H, br, $2NCH_2CH_3$), 5.15 (1H, dd, $^3J_{HH} = 10.7$ Hz, and $^3J_{PH} = 6.5$ Hz, P–CH–CH), 5.76 (1H, dd, $^3J_{HH} = 10.7$ Hz, and $^2J_{PH} = 15.7$ Hz, P–CH–CH), 7.43–7.85 (15H, m, $3C_6H_5$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 12.70 ($2NCH_2CH_3$), 27.14 and 27.74 (2s, $2CMe_3$), 41.63 and 41.71 ($2NCH_2$), 42.47 (P–CH–CH), 42.84 (d, $^1J_{PC} = 49.8$ Hz, P–CH), 80.63 and 83.62 (2C, $2OCMe_3$), 88.57 (d, $^3J_{PC} = 2.1$ Hz, P–C–C–C), 118.49 (d, $^1J_{PC} = 85.2$ Hz, C_{ipso}), 129.33 (d, $^3J_{PC} = 12.9$ Hz, C_{meta}), 133.43 (C_{para}), 134.48 (d, $^2J_{PC} = 9.6$ Hz, C_{ortho}), 160.79 ($O=C-C-C=O$), 165.09 (d, $^2J_{PC} = 1.7$ Hz, $C=O$, ester), 171.82 (d, $^3J_{PC} = 18.1$ Hz, $C=O$, ester), 175.45 ($C=S$). ^{31}P NMR (202.4 MHz, $CDCl_3$): δ 25.31 ((Ph)₃P⁺–C).

REFERENCES

- [1] Katritzky, A. R. *Chem Rev* 2004, 104, 2125.
- [2] Deiters, A.; Martin, S. F. *Chem Rev* 2004, 104, 2199.
- [3] Ishida, M.; Minami, T.; Agawa, T. *J Org Chem* 1979, 44, 2067.
- [4] Schell, P.; Richards, M. P.; Hanson, K.; Berk, S. C.; Makara, G. M. *J Comb Chem* 2005, 7, 69.
- [5] Maghsoodlou, M. T.; Hazeri, N.; Navvabian, H.; Razmjoo, Z.; Marandi, G. *J Chem Res (S)* 2005, 401.
- [6] Maghsoodlou, M. T.; Hazeri, N.; Habibi-Khorassani, S. M.; Solimani, V.; Marandi, G.; Razmjoo, Z. *J Chem Res (S)* 2008, 198.
- [7] Hazeri, N.; Habibi-Khorassani, S. M.; Maghsoodlou, M. T.; Marandi, G.; Nassiri, M.; Ghulame-Shahzadeh, A. *J Chem Res* 2006, 215.
- [8] Roth, H. J.; Kleemann, A. *Pharmaceutical Chemistry*; Ellis Horwood: New York, 1988.
- [9] Korolkovas, A. *Essentials of Medicinal Chemistry*, 2nd ed; Wiley-Interscience: New York, 1988.
- [10] Cobridge, D. E. C. *Phosphorus, An Outline of Chemistry, Biochemistry and Uses*, 5th ed.; Elsevier: Amsterdam, 1995.
- [11] Engel, R. *Synthesis of Carbon-Phosphorus Bond*; CRC Press: Boca Raton, FL, 1998.
- [12] Cadogan, J. I. G. *Organophosphorus Reagents in Organic Synthesis*; Academic Press: New York, 1979.
- [13] Kolodiazhnyi, O. I. *Russ Chem* 1997, 66, 225.
- [14] Bestman, H. J.; Vostrowsky, O. *Top Curr Chem* 1983, 109, 85.
- [15] Hassani, Z.; Islami, M. R.; Sheibani, H.; Kalantari, M.; Saidi, K. *Arkivoc* 2006, i, 89.
- [16] Islami, M. R.; Mollazehi, F.; Badiei, A.; Sheibani, H. *Arkivoc* 2006, xv, 25.

- [17] Kalantari, M.; Islami, M. R.; Hassani, Z.; Saidi, K. *Arkivoc* 2006, x, 55.
- [18] Yavari, I.; Feiz-Javadian, F. *Phosphorus Sulfur Silicon Relat Elem* 2006, 181, 1011.
- [19] Adib, M.; Sayahi, M. H. *Monatsh Chem* 2006, 137, 207.
- [20] Maghsoodlou, M. T.; Hazeri, N.; Habibi-Khorassani, S. M.; Ghulme Shahzadeh, A.; Nassiri, M. *Phosphorus Sulfur Silicon Relat Elem* 2006, 181, 913.
- [21] Maghsoodlou, M. T.; Hazeri, N.; Habibi-Khorassani, S. M.; Nassiri, M.; Marandi, G.; Afshari, G.; Niroumand, U. *Sulfur Chem* 2005, 26, 261.
- [22] Maghsoodlou, M. T.; Hazeri, N.; Habibi-Khorassani, S. M.; Afshari, G.; Nassiri, M. *J Chem Res* 2005, 727.
- [23] Esmaceli, A. A.; Islami, M. R.; Kardan-Moghaddam, G. R. *Phosphorus Sulfur Silicon Relat Elem* 2006, 181, 527.
- [24] Maghsoodlou, M. T.; Habibi-Khorassani, S. M.; Rofouei, M. K.; Adhamdoust, S. R.; Nassiri, M. *Arkivoc* 2006, xii, 145.
- [25] Maghsoodlou, M. T.; Hazeri, N.; Habibi-Khorassani, S. M.; Rofouei, M. K.; Rezaie, M. *Arkivoc* 2006, xiii, 117.
- [26] Siby, A.; Loreau, O.; Taran, F. *Synthesis* 2009, 2365.
- [27] Francois-Endelmond, C.; Carlin, T.; Thuery, P.; Loreau, O.; Taran, F. *Org Lett* 2010, 12, 40.
- [28] Carboni, M.; Gomis, J. M.; Loreau, O.; Taran, F. *Synthesis* 2008, 417.
- [29] Gabillet, S.; Lecercle, D.; Loreau, O.; Dezard, S.; Gomis, J. M.; Taran, F. *Synthesis* 2007, 515.
- [30] Gabillet, S.; Lecercle, D.; Loreau, O.; Carboni, M.; Dezard, S.; Gomis, J. M.; Taran, F. *Org Lett* 2007, 9, 3925.
- [31] Lin, Y.; Bernardi, D.; Doris, E.; Taran, F. *Synlett* 2009, 1466.
- [32] Rueff, J. M.; Barrier, N.; Boudin, S.; Dorcet, V.; Caignaert, V.; Boullay, P.; B.Hix, G.; Jaffres, P. A. *Dalton Trans* 2009, 10614.
- [33] Moonen, K.; Van Meenen, E.; Verwee, A.; Stevens, C. V. *Angew Chem, Int Ed* 2005, 44, 7407.
- [34] Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem Rev* 2004, 104, 6177.
- [35] Maghsoodlou, M. T.; Habibi-Khorassani, S. M.; Hazeri, N.; Nassiri, M. *Phosphorus Sulfur Silicon Relat Elem* 2006, 181, 1363.
- [36] Maghsoodlou, M. T.; Habibi-Khorassani, S. M.; Heydari, R.; Hassankhani, A.; Marandi, G.; Nassiri, M.; Mossadegh, E. *Mol Divers* 2007, 11, 87.
- [37] Saghatforoush, L.; Maghsoodlou, M. T.; Aminkhani, A.; Marandi, G.; Kabiri, R. *J Sulfur Chem* 2006, 27, 583.
- [38] Habibi-Khorassani, S. M.; Maghsoodlou, M. T.; Ebrahimi, A.; Zakarianejad, M.; Fattahi, M. *J Solution Chem* 2007, 36, 1117.
- [39] Habibi-Khorassani, S. M.; Maghsoodlou, M. T.; Ebrahimi, A.; Roohi, H.; Zakarianejad, M.; Moradian, M. *Prog React Kinet Mech* 2005, 30, 127.
- [40] Habibi-Khorassani, S. M.; Maghsoodlou, M. T.; Zakarianejad, M.; Kazemian, M. A.; Nassiri, M.; Karimi, P. *Heteroatom Chem* 2008, 19, 723.
- [41] For chemistry of isocyanides see: (a) Ugi, I. *Angew Chem, Int Ed Engl* 1982, 21, 810; (b) Walborsky, H. M.; Persiasamy, M. P. In *The Chemistry of Functional Groups, Supplement C*, Patai, S.; Rappoport, Z. (Eds.); Wiley: New York, 1983, pp. 835–887; (c) Marcaccini, S.; Torroba, T. *Org Prep Proced Int* 1993, 25, 141.
- [42] Leardini, R.; Nanni, D.; Zanardi, G. *J Org Chem* 2000, 65, 2763.
- [43] Cervinka, O. In *The Chemistry of Enamines*; Rappoport, Z. (Ed.); Part 1. Wiley: New York, 1994, p. 219.
- [44] Günther, H. *NMR Spectroscopy*, 2nd ed.; Wiley: New York, 1995, Ch. 9.
- [45] Anet, F. A. L.; Anet, R. In *Dynamic Nuclear Magnetic Resonance Spectroscopy*; Cotton, F. A.; Jackman, L. M. (Eds.); Academic Press: New York, 1975, p. 543.