Heteroatom Chemistry
Volume 21, Number 4, 2010

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

Ghasem Marandi,[1] Malek Taher Maghsoodlou,[2] Nourallah Hazeri,[2] Reza Heydari,[2] Sayyed Mostafa Habibi Khorassani,[2] Ali Ebrahimi,[2] Sakineh Mollaee Poor,[2] Hassan Hosseini Mahdiabad,[2] Mahmoud Nassiri,[2] and Roya Kabiri[3]

[1]*Department of Chemistry, Faculty of Science, Payame Noor University of Khoy, Khoy, Iran*

[2]*Department of Chemistry, The University of Sistan & Baluchestan, P. O. Box 98135-674, Zahedan, Iran*

[3]*Faculty of Chemistry, The University of Tabriz, Tabriz, Iran*

Received 14 November 2009; revised 13 March 2010

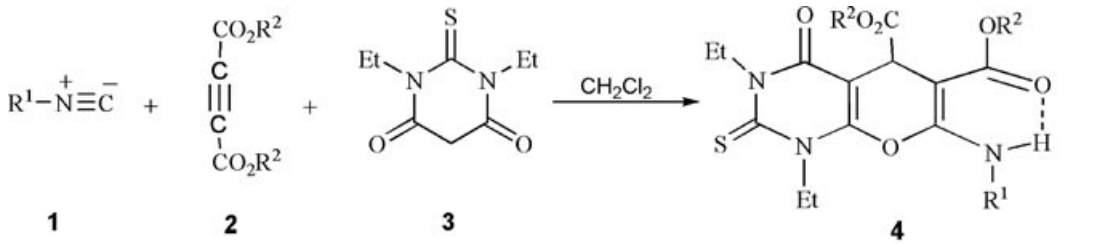
ABSTRACT: *In a series of separate experiments reaction between N,N′-diethyl-2-thiobarbituric acid and acetylenic diesters in the presence of isocyanides or triphenylphosphine led to highly functionalized 4H-pyrano[2,3-d]thiopyrimidine or 1,4-di-ionic organophosphorus derivatives. The ^{1}H NMR spectra of diethyl-7-(2,6-dimethylphenylamino)-4-oxo-2-thio-1,3-diethyl-4H-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 ($\Delta G^{\neq}$) for this process is about 54.85 ± 2 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 Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20601

Correspondence to: Malek Taher Maghsoodlou; e-mail: mt_maghsoodlou@yahoo.com.

Contract grant sponsor: Research Council of the University of Sistan & Baluchestan.

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



1 **2** **3** **4**

4	R^1	R^2	Yield (%)
a	Bu^t	Me	95
b	cyclohexyl	Me	87
c	cyclohexyl	Bu^t	92
d	2, 6-Me_2-phenyl	Et	90

SCHEME 1

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

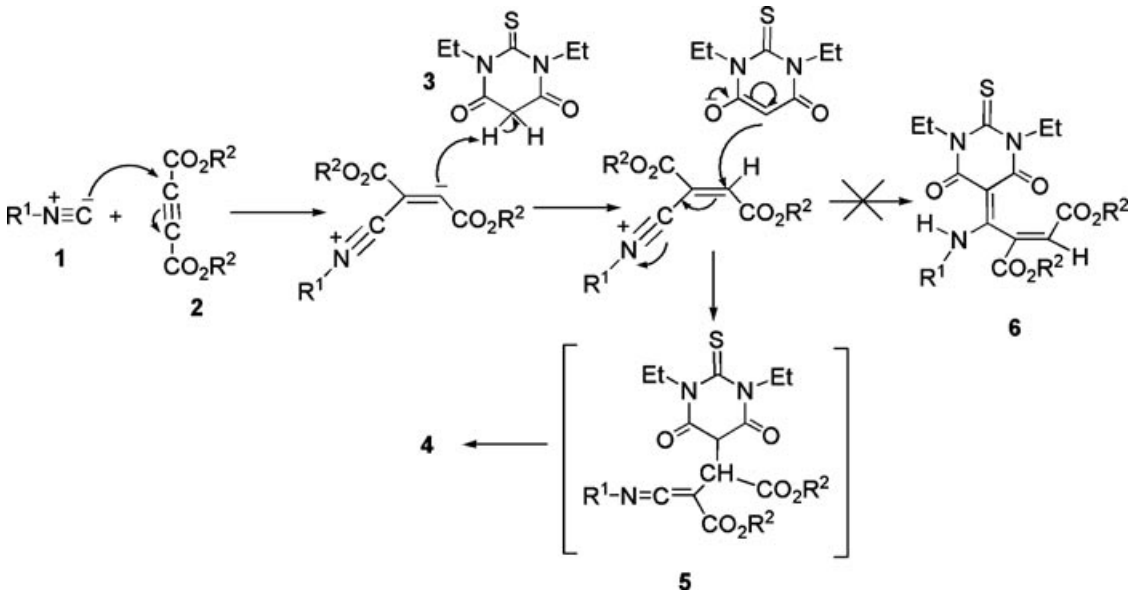
In the set of investigations made on the development of heterocyclic and organophosphorus compound synthesis [35–40], we now describe a one-pot, synthesis of *N,N′*-diethyl-2-thiobarbituric acid containing heterocyclic **4** and organophosphorus derivatives **9** using isocyanides **1** or triphenylphosphine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

RESULTS AND DISCUSSION

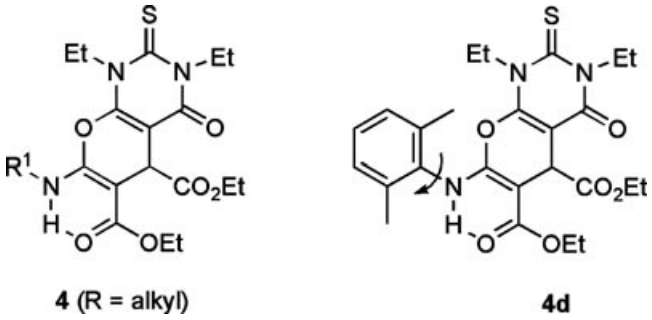
The reaction between alkyl or aryl isocyanides **1** and electron-deficient acetylenic esters **2** in the presence of strong CH-acid **3** proceeded at ambient temperature in CH_2Cl_2 and was completed within 5 days. The structure of **4** was assigned on the basis of elemental analyses, infrared (IR), ^1H, ^{13}C 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 (δ = 1.26 and 1.40), *tert*-butyl (δ = 1.44), methoxy (δ = 3.68 and 3.71), methylene (δ = 4.50 and 4.57), methine (δ = 4.58), and a broad band for the NH group at δ = 8.99 ppm, indicating intramolecular hydrogen bond formation with the vicinal carbonyl group.

The ^{13}C 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-Me_2 groups in both ^1H and ^{13}C 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-Me_2 protons coalesce near 90°C and appear as a fairly sharp symmetrical resonance at 110°C. No further



SCHEME 2



SCHEME 3

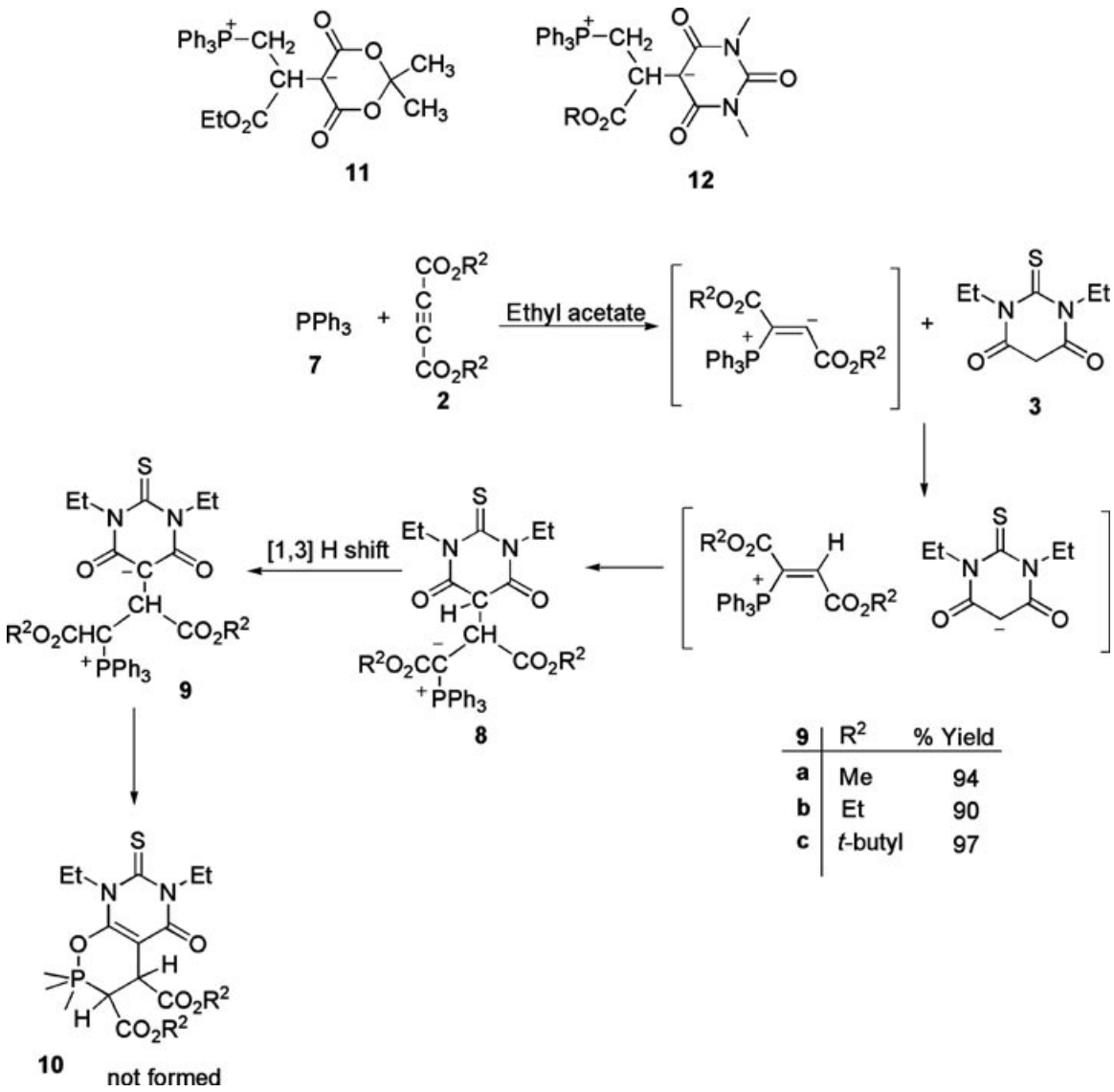
dynamic NMR effect was observed up to 120°C, as the highest temperature investigated.

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 ($\Delta G^{\neq}$) 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 $\Delta H^{\neq}$ and $\Delta S^{\neq}$, even though the errors in $\Delta G^{\neq}$ 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, ^{1}H, ^{13}C, and ^{31}P 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**.

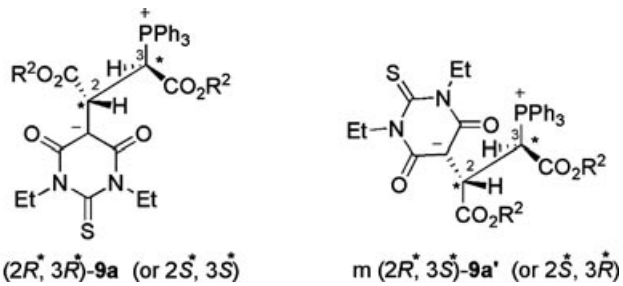
TABLE 1 First-Order Rate Constants, Standard *Gibbs* Energies, and Selected Activation Parameters for **4d** in 1,2-Dichlorobenzene

Compound	*T*(°*C*)	*Ar-Me* (δ, *ppm*)		Δν *(Hz)*	*K*(s^{-1})	T_c(°*K*)	$\Delta G^{\neq}$(*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 ^{31}P NMR spectroscopic data ($\delta = 23$–25), which is in agreement with the presence of a Ph_3P^+-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 triphenylphosine 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-diionic compound **9**.



SCHEME 5

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

($^3J_{HH}$) 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 $^3J_{HH}$ 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, $^3J_{PC}$. 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 $^3J_{PC}$ of 11–15 Hz for the $C(CO)_2$ group is in agreement with the (2R^*,3R^*)-**9** for the major diastereoisomer (see the Experimental section). On the other hand, the measurement of $^3J_{PC}$ of 18–20 Hz for the ester C=O group is in accord with the (2R*,3S^*)-**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 ^{1}H 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, ^{1}H, ^{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). ^{1}H 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, $2NCH_2CH_3$), 4.58 (1H, s, CH), 8.99 (1H, br s, NH···O=C). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 11.31 and 12.90 ($2OCH_2CH_3$), 30.40 ($NCMe_3$), 35.60 (CH), 43.84 and 44.67 ($2NCH_2CH_3$), 52.83 (CMe_3), 51.44 and 52.57 ($2OCH_3$), 74.21 and 92.99 (2C=C—O), 151.41 (C=S), 158.94 and 159.07 (2C=C—O), 169.27 (NCO), 173.56 and 174.98 (2C=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 $C_{19}H_{27}N_3O_6S$ (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). ^{1}H 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 O—CH_3), 4.32–4.60 (4H, m, $2NCH_2CH_3$), 4.58 (1H, s, CH), 8.62 and 8.64 (1H, d, NH···O=C). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 11.36 and 12.75 ($2NCH_2CH_3$), 24.47, 25.18, 33.69, 33.95, and 35.67 (5CH_2 of cyclohexyl), 35.70 (CH), 43.81 and 44.94 ($2NCH_2CH_3$), 51.12 (N—CH), 51.33 and 52.63 ($2OCH_3$), 72.77 and 92.92 (2C=C—O), 151.43 (C=S), 157.59 and 159.08 (2C=C—O), 169.05 (NCO), 173.60, 175.08 (2C=O). MS (*m/z*, %): 451 (M^+, 2), 392 (100), 305 (23), 223 (38), 163 (29), 59 (36), 55 (95), 41 (61). Anal Calcd for $C_{21}H_{29}N_3O_6S$ (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-oxo2-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) (ν_{max}, cm^{-1}): 3300 (N—H); 1686, 1717 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 1.26 –1.85 (10H, m, $5CH_2$), 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, $2CMe_3$), 3.54 (1H, m, N—CH), 4.45 (1H, s, CH), 4.56 and 4.60 (4H, m, $2NCH_2CH_3$), 8.58 (1H, s, NH···O=C). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 11.41 and 12.73 ($2NCH_2CH_3$), 24.75 and 25.26 ($2CH_2$ of cyclohexyl), 28.00 and 28.48 (6 Me of $2CMe_3$), 27.80, 33.90, and 34.15 (3 CH_2 of cyclohexyl), 37.25 (CH), 43.72 and 44.90 ($2NCH_2CH_3$), 51.21 (N—CH), 80.27 and 81.25 ($2CMe_3$), 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 $C_{27}H_{41}N_3O_6S$ (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) (ν_{max}, cm^{-1}): 3245 (N—H); 1693, 1734 (C=O). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 0.73 (3H, t, J = 6.5 Hz, $N—CH_2CH_3$), 1.25 (3H, t, J = 6.5 Hz, $N—CH_2CH_3$), 1.23–1.42 (6H, m, $2OCH_2CH_3$), 2.24 and 2.35 (6H, 2s, $ArMe_2$), 3.90–4.24 (4H, m, $2OCH_2CH_3$), 4.25–4.52 (4H, m, $N-CH_2CH_3$), 4.68 (1H, s, CH), 7.10–7.21 (3H, m, ArH), 7.28 (1H, s, NH···O=C). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ_C 11.34 and 11.95 ($2NCH_2CH_3$), 14.16 and 14.35 ($2OCH_2CH_3$), 18.25 and 18.36 ($ArMe_2$), 36.06 (CH), 43.70 and 44.87 ($2NCH_2CH_3$), 60.38 and 61.41 ($2OCH_2CH_3$), 74.81 and 92.78 (2C=C—O), 128.03, 128.19, 128.37, 133.78, 136.04, and 137.04 ($6C_{arom}$), 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 $C_{25}H_{31}N_3O_6S$ (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 × 5 mL) to give a cream powder. Yield 0.57 g, 94%. m.p 160–162°C; IR (KBr) (ν_{max}, cm^{-1}): 1734, 1741, and 1749 (C=O). MS (*m/z, %*): 604 (M^+, 3), 546 (M-2Et, 42), 486 (M-$2CO_2Me$, 37), 406 (M—$C_8H_{10}N_2O_2S$, 27), 262 (Ph_3P, 81), 183 (Ph_2P, 100), 108 (PhP, 42), 77 (Ph, 29). Anal. Calcd. for $C_{32}H_{33}O_6N_2SP$ (604.65): C, 63.56; H, 5.50; N, 4.63. Found: C, 63.61; H, 5.57; N, 4.60.

Major isomer. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.29 (6H, t, $^3J_{HH}$ = 6.9 Hz, 2 NCH_2CH_3) , 3.18, 3.30 (6H, 2s, $2OCH_3$), 4.56 (4H, m, $2ABX_3$ system $2NCH_2CH_3$), 5.02 (1H, dd, $^3J_{HH}$ = 10.5 Hz and $^3J_{PH}$ = 6.6 Hz, P—CH—CH), 5.80 (1H, dd, $^3J_{HH}$ = 10.5 Hz and $^2J_{PH}$ = 14.5 Hz, P—CH—CH), 7.53–7.87 (15H, m, $3C_6H_5$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 12.78 ($2NCH_2CH_3$), 41.55 and 41.60 ($2NCH_2$), 42.54 (d, $^2J_{PC}$ = 4.7 Hz, P—CH—CH), 43.33 (d, $^1J_{PC}$ = 41.6 Hz, P—CH), 52.71 and 52.93 ($2OCH_3$), 87.71 (d, $^3J_{PC}$ = 11.2 Hz, P—C—C—C), 120.76 (d, $^1J_{PC}$ = 88.0 Hz, C_{ipso}), 129.54 (d, $^3J_{PC}$ = 12.9 Hz, C_{meta}), 134.12 (C_{para}), 134.28 (d, $^2J_{PC}$ = 9.5 Hz, C_{ortho}), 161.14 (O=C—C—C=O), 166.88 and 173.74 (2C=O, ester), 176.09 (C=S). ^{31}P NMR (202.4 MHz, $CDCl_3$): δ 24.28 ($(Ph)_3P^+$—C).

Minor isomer. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.17 (6H, t, $^3J_{HH}$ = 6.9 Hz, $2NCH_2CH_3$), 3.31, 3.59 (6H, 2s, $2OCH_3$), 4.20 (4H, m, $2ABX_3$ system $2NCH_2CH_3$), 5.09 (1H, dd, $^3J_{HH}$ = 11.3 Hz and $^3J_{PH}$ = 7.0 Hz, P—CH—CH), 5.84 (1H, dd, $^3J_{HH}$ = 11.3 Hz and $^2J_{PH}$ = 15.2 Hz, P—CH—CH), 7.53–7.87 ($15H_{aro}$, m, $3C_6H_5$);^{13}C NMR (125.8 MHz, $CDCl_3$): δ 12.78 ($2NCH_2CH_3$), 42.01 and 42.18 ($2NCH_2$), 42.46 (P—CH—CH), 43.18 (d, $^1J_{PC}$ = 50.8 Hz, P—CH), 52.55 and 52.71 ($2OCH_3$), 87.99 (d, $^3J_{PC}$ = 2.5 Hz, P—C—C—C), 120.78 (d, $^1J_{PC}$ = 86.3 Hz, C_{ipso}), 129.51 (d, $^3J_{PC}$ = 12.9 Hz, C_{meta}), 134.08 (C_{para}), 134.28 (d, $^2J_{PC}$ = 9.5 Hz, C_{ortho}), 161.03 (O=C—C—C=O), 167.33 (d, $^2J_{PC}$ = 1.7 Hz, C=O, ester), 173.17 (d, $^3J_{PC}$ = 18.0 Hz, C=O, ester), 175.69 (C=S). ^{31}P NMR (202.4 MHz, $CDCl_3$): δ 23.97 ($(Ph)_3P^+$—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) (ν_{max}, cm^{-1}): 1728, 1735, and 1746 (C=O). MS (*m/z, %*): 632 (M^+, 5), 574 (M-2Et, 23), 486 (M-$2CO_2Et$, 36), 449 (M-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. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 0.87–1.32 (12H, m, 2OCH$_2$*CH*$_3$ and 2NCH$_2$*CH*$_3$), 3.61 and 3.78 (4H, 2m, 2ABX$_3$ system, 2O*CH*$_2$CH$_3$), 4.61 (4H, m, ABX$_3$ system 2N*CH*$_2$CH$_3$), 5.29 (1H, br, P–CH–C*H*), 5.66 (1H, br, P–C*H*–CH), 7.48–7.90 (15H, m, 3C$_6$H$_5$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 12.72 (2NCH$_2$*CH*$_3$), 13.56 and 13.79 (2OCH$_2$*CH*$_3$), 41.60 and 41.66 (2NCH$_2$), 42.58 (d, $^2J_{PC}$ = 4.5 Hz, P–CH–*C*H), 43.38 (d, $^1J_{PC}$ = 43.3 Hz, P–*C*H), 61.81 and 62.62 (2O*CH*$_2$CH$_3$), 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 (2C=O, ester), 176.05 (C=S). ^{31}P NMR (202.4 MHz, $CDCl_3$): δ 24.28 ((Ph)$_3$P$^+$–C).

Minor isomer. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 0.87–1.32 (12H, m, 2OCH$_2$*CH*$_3$ and 2NCH$_2$*CH*$_3$), 3.61 and 3.78 (4H, 2m, 2ABX$_3$ system, 2O*CH*$_2$CH$_3$), 4.21 (4H, m, ABX$_3$ system, 2N*CH*$_2$CH$_3$), 5.07 (1H, dd, $^3J_{HH}$ = 11.0 Hz and $^3J_{PH}$ = 6.0 Hz, P–CH–C*H*), 5.90 (1H, dd, $^3J_{HH}$ = 11.0 Hz and $^3J_{PH}$ = 13.2 Hz, P–C*H*–CH), 7.48–7.90 (15H, m, 3C$_6$H$_5$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.31 (2NCH$_2$*CH*$_3$), 14.05 and 14.19 (2OCH$_2$*CH*$_3$), 41.91 and 41.98 (2NCH$_2$), 42.49 (d, $^2J_{PC}$ = 4.6 Hz, P–CH–*C*H), 42.66 (d, $^1J_{PC}$ = 50.3 Hz, P–CH), 61.33 and 62.23 (2O*CH*$_2$CH$_3$), 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)$_3$P$^+$–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$_2$CMe$_3$, 29), 490 (M–C$_8$H$_{10}$N$_2$O$_2$S, 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. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 0.94 and 0.99 (18H, 2s, 2C*Me*3), 1.07–1.23 (6H, br, 2NCH$_2$*CH*$_3$), 4.56 (4H, br, 2N*CH*$_2$CH$_3$), 4.85 (1H, dd, $^3J_{HH}$ = 10.4 Hz,$^3J_{PH}$ = 6.2 HZ, P–CH–C*H*), 5.64 (1H, dd, $^3J_{HH}$ = 10.4 Hz, $^2J_{PH}$ = 13.9 Hz, P–C*H*–CH), 7.43–7.85 (15H, m, 3C$_6$H$_5$);^{13}C NMR (125.8 MHz, $CDCl_3$): δ 12.70 (2NCH$_2$*CH*$_3$), 27.05 and 27.36 (2s, 2C*Me*$_3$), 41.31 and 42.17 (2NCH$_2$), 42.42 (d, $^2J_{PC}$ = 4.7 Hz, P–CH–*C*H), 43.45 (d, $^1J_{PC}$ = 42.9 Hz, P–*C*H), 81.63 and 84.01 (2C, 2O*C*Me$_3$), 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)$_3$P$^+$–C).

Minor isomer. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 1.02 and 1.27 (18H, 2s, 2C*Me*3), 1.07–1.23 (6H, br, 2NCH$_2$*CH*$_3$), 4.18 (4H, br, 2N*CH*$_2$CH$_3$), 5.15 (1H, dd, $^3J_{HH}$ = 10.7 Hz, and $^3J_{PH}$ = 6.5 Hz, P–CH–C*H*), 5.76 (1H, dd, $^3J_{HH}$ = 10.7 Hz, and $^2J_{PH}$ = 15.7 Hz, P–C*H*–CH), 7.43–7.85 (15H, m, 3C$_6$H$_5$);^{13}C NMR (125.8 MHz, $CDCl_3$): δ 12.70 (2NCH$_2$*CH*$_3$), 27.14 and 27.74 (2s, 2C*Me*$_3$), 41.63 and 41.71 (2NCH$_2$), 42.47 (P–CH–*C*H), 42.84 (d, $^1J_{PC}$ = 49.8 Hz, P–CH), 80.63 and 83.62 (2C, 2O*C*Me$_3$), 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)$_3$P$^+$–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] Esmaeili, 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. Syntheis 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.