Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 8868

www.rsc.org/obc

PAPER

1,2,4-Dithiazole-5-ones and 5-thiones as efficient sulfurizing agents of phosphorus(III) compounds – a kinetic comparative study†‡§

Oleksandr Ponomarov,[a] Andrew P. Laws[b] and Jiří Hanusek*[a]

Received 26th July 2012, Accepted 24th September 2012
DOI: 10.1039/c2ob26460a

The sulfurization efficiency of 25 3-substituted-1,2,4-dithiazole-5-ones and 5-thiones towards triphenyl phosphite in acetonitrile, DCM, THF and toluene at 25 °C was evaluated. All the 1,2,4-dithiazoles are much better sulfurizing reagents than commercially available agents (PADS, TETD, Beaucage's reagent). The most efficient sulfurizing agents in all solvents are 3-phenoxy (**4**), 3-phenylthio (**5**) and 3-ethoxy-1,2,4-dithiazole-5-one (**1**) whose reactivity is at least two orders of magnitude higher than that of other 1,2,4-dithiazoles. Contrary to a previous report, the sulfurization with **1** does not yield carbonylsulfide and ethyl cyanate as the additional reaction products but unstable ethoxythiocarbonyl isocyanate which has been trapped with 4-methoxyaniline. Similar trapping experiments have proven that the site of attack is at the sulfur adjacent to the C═O group for compounds **4** and **5**. The reaction pathway involves rate-limiting initial nucleophilic attack of the phosphorus at sulfur followed by decomposition of the phosphonium intermediate to the corresponding phosphorothioate and isocyanate/isothiocyanate species. The existence of the phosphonium intermediate during sulfurization of triphenyl phosphine with 3-phenyl-1,2,4-dithiazole-5-thione (**7a**) was proven using kinetic studies. From the Hammett and Brønsted correlations and from other kinetic measurements it was concluded that the transition-state structure is almost apolar for the most reactive 1,2,4-dithiazoles whereas a polar structure resembling a zwitter-ionic intermediate may be more appropriate for the least reactive 1,2,4-dithiazoles. The extent of P–S bond formation and S–S bond cleavage is very similar in all reaction series but it gradually decreases with the reactivity of the 1,2,4-dithiazole derivatives.

Introduction

There is an increasing use of phosphorothioate analogues of oligonucleotides in nucleic acid research.[1] Therefore, the synthesis of oligonucleotide phosphorothioate analogues is of considerable interest. One of the key steps in the synthesis of phosphorothioate oligoribonucleotides is the replacement of the oxygen by sulfur. A number of reagents have been designed and tested in recent years for sulfurization of phosphorus(III) compounds from which those based on the 1,2,4-dithiazole skeleton[2] appear to be advantageous alternatives to existing sulfurizing reagents.[3] Even 1,2,4-dithiazole-5-ones† containing a chiral side chain were recently synthesized and tested for diastereoselective sulfurization of dinucleotide phosphite triesters.[4] However, no comparative study of their sulfurization efficiency including reactivity, stability and solubility has been published until now.

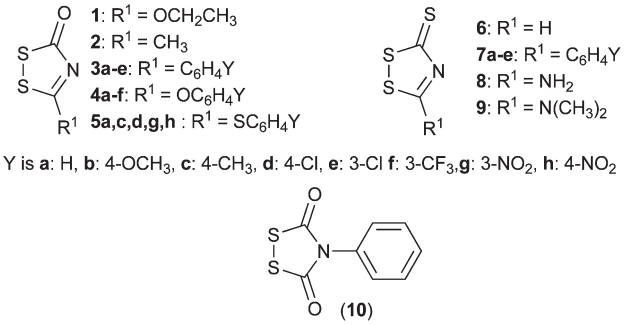
In the first part of the current study, we have compared the reactivity of 26 known 1,2,4-dithiazoles *i.e.* 3-ethoxy-1,2,4-dithiazole-5-one (**1**) (EDITH), 3-methyl-1,2,4-dithiazole-5-one (**2**) (MEDITH), 3-(substituted-phenyl)-1,2,4-dithiazole-5-ones (**3a–e**), 3-(substituted-phenoxy)-1,2,4-dithiazole-5-ones (**4a–f**), 3-(substituted-phenylthio)-1,2,4-dithiazole-5-one (**5a–h**), 1,2,4-dithiazole-5-thione (**6**), 3-(substituted-phenyl)-1,2,4-dithiazole-5-thione (**7a–e**), 3-amino-1,2,4-dithiazole-5-thione (**8**) (ADTT, xanthane hydride), 3-dimethylamino-1,2,4-dithiazole-5-thione (**9**) and 4-phenyl-1,2,4-dithiazole-3,5-dione (**10**) (Scheme 1) towards triphenyl phosphite and triethyl phosphite as model

[a]*University of Pardubice, Faculty of Chemical Technology, Institute of Organic Chemistry and Technology, Studentská 573, 532 10 Pardubice, The Czech Republic. E-mail: Jiri.Hanusek@upce.cz; Fax: +420 466 037 068; Tel: +420 466 037 015*
[b]*University of Huddersfield, Department of Chemical and Biological Sciences, Queensgate HD1 3DH, Huddersfield, United Kingdom. E-mail: a.p.laws@hud.ac.uk*

† The nomenclature and numbering of the 1,2,4-dithiazole ring differ throughout the cited literature. According to IUPAC rules the C═O (C═S) group should have lower locant 3- instead of 5- (as seen *e.g.* in ref. 2*f*, 4, 7, 8 and 10). Unfortunately in newer literature (*e.g.* ref. 2*a–e*, 5 and 12) incorrect numbering was adopted, therefore we decided to keep this numbering in our previous papers (ref. 11*a*,*b* and 35*d*) as well as in the present paper to avoid misunderstanding when comparing results.

‡ Dedicated to Professor Vojeslav Štěrba on the occasion of his 90th birthday.

§ Electronic supplementary information (ESI) available: Observed rate constants and NMR spectra. See DOI: 10.1039/c2ob26460a



Scheme 1

P(III) compounds in acetonitrile, dichloromethane, toluene and tetrahydrofuran at 25 °C.

In the second part of this paper we report the structure of the by-products formed during the sulfurization reaction using 3-ethoxy-1,2,4-dithiazole-5-one (**1**), 3-phenoxy-1,2,4-dithiazole-5-one (**4a**) and 3-phenylthio-1,2,4-dithiazole-5-one (**5a**) and the detailed reaction mechanism of the sulfurization using substituted derivatives.

Results and discussion

Evaluation of 1,2,4-dithiazoles (1–10) for sulfurization of triphenyl and triethyl phosphites

It is important that an efficient sulfur transfer reagent is used for the synthesis of oligonucleotide phosphorothioates; J.-Y. Tang's group has shown[2c–e,5] that various 1,2,4-dithiazole-5-ones and thiones have potential as sulfurizing reagents. Using a HPLC technique, they qualitatively compared the efficiency of various sulfurizing reagents towards the dimer 5′-d(TsT)-3′ and 25mer (5′-CTCTCGCACCCATCTCTCTCCTTCT-3′) oligonucleotide and found EDITH (**1**) to be the most efficient. However, oligonucleotides are not suitable for kinetic measurements due to their low stability. Therefore similar P(III) compounds – phosphites – were used as a model in our study. Unfortunately, in some cases the reaction of trialkyl phosphites which best resemble oligonucleotides is too fast and therefore less reactive triphenyl phosphite[3i] has been chosen as a suitable P(III) compound whose sulfurization can be easily followed spectrophotometrically.

Using ^{31}P NMR we have found that the reaction of all 1,2,4-dithiazoles **1–10** with triphenyl phosphite proceeds smoothly and the only product is triphenyl phosphorothioate.

Studies of the reactions using ^{31}P NMR provided no evidence for the formation of tetra- or pentacoordinate intermediates; if such species exists on the reaction coordinate, then their concentration must be negligible. The corresponding isocyanate/isothiocyanate species (see below) are formed as initial reactive by-products which subsequently undergo consecutive reactions with nucleophilic species.

The kinetics of the sulfurization reaction of both triethyl and triphenyl phosphites were determined by monitoring the decrease in concentration of **1–10** spectrophotometrically at an appropriate wavelength in various solvents under pseudo-first order conditions (phosphites in large excess). For comparison we have also measured the kinetics of sulfurization of triphenyl and triethyl phosphites with commercially available phenylacetyl disulfide (PADS), tetraethylthiuram disulfide (TETD) and Beaucage's reagent in $CDCl_3$ or CD_3CN (^{31}P NMR study). For each of the systems, the absorbance decreased exponentially with time (see ESI§) from which was obtained a pseudo-first order rate constant. In all cases the dependences of the observed rate constant *vs.* phosphite concentration were linear and their slopes gave second-order rate constants *k* (Table 1).

The rate and efficiency of sulfurization are sometimes very dependent on the solvent system,[6] therefore we studied kinetics in three solvents that are routinely used for the synthesis of oligonucleotide phosphorothioates *i.e.* in acetonitrile (ACN), dichloromethane (DCM) and tetrahydrofuran (THF). Some kinetics were also measured in toluene in order to compare the second-order rate constants with those obtained for elemental sulfur.

All the compounds **1–10** were found to be much better sulfurizing reagents in comparison with commercially available agents. Also, their stability is very good – almost all of them can be stored at room temperature for a couple of months with the only exception[7] of MEDITH. The solubility of **1–10** in the most common solvent – acetonitrile – is in most cases very good. Only xanthane hydride and its dimethyl derivative are sparingly soluble in this solvent.

From inspection of the results presented in Table 1 it is clear that the most efficient sulfurizing agents, in all solvents, are 3-phenoxy-1,2,4-dithiazole-5-ones (**4a–f**) which are in most cases more than two orders of magnitude more reactive than other 1,2,4-dithiazole-5-ones and thiones.

Site of attack

Both the site of attack on the 1,2,4-dithiazole skeleton and the by-products formed during sulfurization of P(III) compounds have been established previously in various solvents[7–9] or without solvent.[10] In solvent, the corresponding thioacyl isothiocyanate, thioacyl isocyanate or isocyanate were exclusively formed;[7–9] *i.e.* the reaction pathway involved initial nucleophilic attack of the phosphorus at the sulfur adjacent to the C=O (C=S) group followed by decomposition of the phosphonium intermediate to products (Scheme 2).

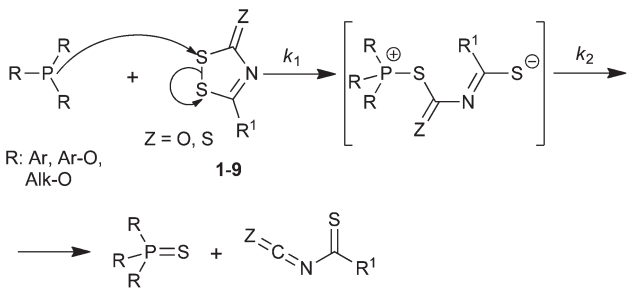
In our previous papers[11] we have dealt with the by-products and the mechanism of the sulfurization of phosphines and phosphites using 3-amino-1,2,4-dithiazole-5-thione (**8**) and its *N*,*N*-dimethylderivative (**9**). Contrary to previous reports,[1g,2d,e] the sulfurization of triphenyl phosphines and trialkyl phosphites by **8** and **9** does not yield carbon disulfide and cyanamide as the additional reaction products but reactive thiocarbamoyl isothiocyanates (Scheme 2) which have been trapped with external nucleophiles.

The results above contradict the report of the production of triphenyl phosphorothioate, *O*-ethyl cyanate and carbonylsulfide[2a,12] as products from the reaction of EDITH (**1**) with triphenyl phosphite. Therefore we have tried to elucidate the structure of the by-products formed during the reaction of **1** with triphenyl phosphite and thus prove or disprove the suggestion that the site of attack of the 1,2,4-dithiazole skeleton is at sulfur S-2.

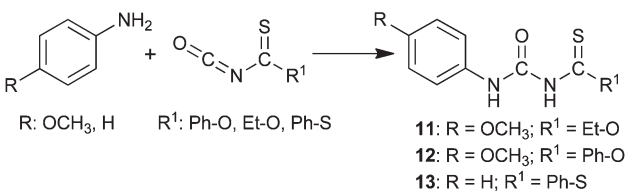
Table 1 Second-order rate constants k (l mol^{-1} s^{-1}) for the reaction of sulfurization reagents **1–10**, PADS, TETD, Beaucage's agent and S_8 with triphenyl phosphite (or triethyl phosphite, see the final column) in acetonitrile (ACN), dichloromethane (DCM), tetrahydrofuran (THF) and toluene at 25 °C measured at an appropriate wavelength λ (nm)

Sulfurization agent	λ (nm)	Solubility in ACN	k (ACN)	k (DCM)	k (THF)	k (toluene)	k $(EtO)_3P$ (ACN)
1	290	1 g/20 ml	597 (877)[a]	432 (483)[a]	347	550	—[f]
2	320	1 g/5 ml	2.03	2.11	1.62	1.87	39 170
3a	350	1 g/10 ml	10.64	3.97	4.48	5.51	—[f]
3b	390	—	7.11	3.13	1.61	5.55	—[f]
3c	365	—	7.83	3.02	2.52	4.12	—[f]
3d	335	—	26.3	12.3	10.8	22.6	—[f]
3e	365	—	31.0	17.8	21.4	28.0	—[f]
4a	327	1 g/250 ml	2 430	1 882	1 125	3 626	—[f]
4b	327	—	1 587	909	720.9	2 362	—[f]
4c	327	—	2 306	1 550	1 148	2 515	—[f]
4d	327	—	3 630	3 184	2 141	5 843	—[f]
4e	325	—	3 932	3 475	2 333	5 907	—[f]
4f	331	—	4 372	4 283	2 624	6 737	—[f]
5a	340	—	384	238	239	426	—[f]
5c	320	—	327	187	196	259	—[f]
5d	340	—	748	538	415	829	—[f]
5g	340	—	1 515	1 870	1369	3807	—[f]
5h	340	—	1 576	2 022	1335	4374	—[f]
6	400	1 g/100 ml	0.1236[b]	0.1778	0.0152	0.0691	1 408
7a	425	1 g/150 ml	0.0828	0.0222	0.0266	0.0310	3 570[b]
7b	450	—	0.0571	0.0184	0.0250	0.0196	—
7c	460	—	0.0524	0.0158	0.0179	0.0167	—
7d	450	—	0.2325	0.0909	0.0722	0.0997	—
7e	450	—	0.3566	0.1155	0.1139	0.1530	—
8	360	1 g/450 ml	2.65	Insoluble	0.275	Insoluble	3 122[a]
9	365	1 g/110 ml	2.62 (3.26)[a]	2.37	0.99[b]	1.71	2 500
10	290	1 g/15 ml	0.025	0.017	0.014	0.023	—
PADS	[c]	1 g/110 ml	—	No reaction[c,d]	—	—	0.069[d]
TETD	[c]	1 g/ 12 ml	No reaction[c]	No reaction[c,d]	—	—	—
Beaucage's agent	[c]	—	0.000758[c]	0.00653[c,d]	—	—	—
S_8	—	—	—	—	—	No reaction[e]	0.0096[e]

[a] At 30 °C. [b] Consecutive reaction of the isocyanate/isothiocyanate by-product with traces of water in solvent appears. [c] Measured by ^{31}P NMR. [d] In $CDCl_3$ at 25 °C. [e] In toluene at 31 °C (from ref. 14*c*). [f] Reaction is too fast for stopped-flow measurements.



Scheme 2



Scheme 3

To prove the presence of the anticipated ethoxythiocarbonyl isocyanate during the course of the sulfurization reaction (*cf.* Scheme 2) we added an external nucleophile, 4-methoxyaniline, to the reaction mixture to act as a trap. After the reaction work-up, *O*-ethyl *N*-[(4-methoxyphenyl)carbamoyl]thiocarbamate (**11**) was obtained in very good yield (96%) which is the analogous product of known nucleophilic addition of aniline to ethoxythiocarbonyl isothiocyanate.[13a] A similar experiment (according to ref.[13b]) was carried out with our original 3-phenoxy-1,2,4-dithiazole-5-one (**4a**) and 3-phenylthio-1,2,4-dithiazole-5-one (**5a**) which provided *O*-phenyl *N*-[(4-methoxyphenyl)carbamoyl]-thiocarbamate (**12**) or phenyl *N*-(phenylcarbamoyl)dithiocarbamate (**13**), respectively, under the same conditions (Scheme 3).

These observations prove that the site of attack is at the sulfur adjacent to the C=O group for the 1,2,4-dithiazoles **1**, **4** and **5**.

Reaction mechanism

The detailed mechanism of sulfurization of various phosphorus(III) compounds (phosphines, phosphites, phosphonites, phosphinites and phosphorous triamides) by sulfur,[14] disulfides,[15] trisulfides[16] and tetrasulfides[17] has been briefly studied in the past. In all cases it was concluded that the reaction involves rate-limiting nucleophilic attack of phosphorus on sulfur producing a

phosphonium salt intermediate which then quickly decomposes to the corresponding product containing a P=S group. The high negative Hammett ρ-values[14a,c] obtained for the reaction of *m*- and *p*-substituted triphenyl phosphines, phosphonites and phosphinites with elemental sulfur ($\rho = -2.5 \div -3$) are also consistent with a highly polarized transition state. On the other hand, the corresponding ρ-values obtained using diphenyltrisulfide as the sulfurizing agent are only around $\rho = -1.1$ for all above-mentioned P(III) compounds. This indicates only a moderate degree of a positive charge build-up on phosphorus and the same degree of a negative charge on sulfur (as seen from $\rho = +1$ obtained for the reaction of *p*-substituted diphenyltrisulfides with triphenylphosphine[16c]) in the transition state. On the other hand the reaction of thiiranes (episulfides) with triphenyl phosphine producing alkenes and triphenyl phosphine sulfide is considered to proceed through a non-polar transition state[18] because of its insensitivity to large changes in solvent polarity and its stereospecificity.

The position of the transition state on the reaction coordinate and the charge on the transition state can be determined from studies of the effect of solvent polarity on reaction rates. In the case of 1,2,4-dithiazoles the influence of solvent polarity (see Table 1) or proton donor ability[11b] on the rate of sulfurization is only negligible. Also the Hammett ρ-values for the reaction of *m*- and *p*-substituted triphenyl phosphites with **3a** or **7a** and **4a** or **5a** (see Fig. 1 and ESI§) in acetonitrile range from −1.3 to −0.7, respectively (*cf.* also with value −1.1 observed for **8**)[11b] which together with the high and negative entropy of activation[11b] is consistent with a bimolecular association step (k_1) leading to the transition state. It appears that the gradual change in ρ-values is in accordance with reactivity–selectivity principle.[19] The gradual increase in reactivity (**7a** < **3a** < **5a** < **4a**) is accompanied by a decrease in selectivity measured by the proportionality factor ρ (absolute ρ-value gradually decreases from *ca*. 1.3 to 0.7). The transition-state structure is therefore assumed to become closer to that of the reactant state as the energy barrier decreases.[19] In other words the transition state for the most reactive **4a** is looser than that for the least reactive **7a** (*i.e.* the P–S bond is formed to somewhat less extent for **4a** than in the case of **7a**). The interpretation of the Hammett ρ-value in terms of absolute charge distribution in the transition state requires a reference reaction, ideally a corresponding ρ-value for an equilibrium reaction. Unfortunately, the only equilibrium studied for P(III) compounds concerns protonation of phosphines in nitromethane which gave[20] Taft $\rho^* = -2.6$. Although the corresponding values for phosphites are unknown, similar or slightly smaller values might be expected given that the reaction of **8** with triphenyl phosphines as well as phosphites gave[11b] similar ρ-values. Given that the ρ-values were relatively small it can be concluded that there is only a small positive charge on phosphorus in the transition state.

To get a better insight into the reaction mechanism, especially into the extent of S–S bond cleavage in the transition state, we also studied the transmission of polar substituent effects in four series of substituted 1,2,4-dithiazoles: **3a–e**, **4a–f**, **5a,c,d,g,h** and **7a–e**.

In two series 3-(subst.phenyl)-1,2,4-dithiazol-5-ones (**3a–e**) and 3-(subst.phenyl)-1,2,4-dithiazol-5-thiones (**7a–e**) the second-order rate constants for the reaction with triphenyl phosphite were measured in acetonitrile at 25 °C and then plotted against the pK_a of the thiobenzamides to generate a Brønsted-type relationship, whose slope gives β'_{lg} reflecting the progress of S–S bond cleavage in the transition state (Fig. 2).

For all four series the rate constants were also plotted against the substituent σ-values (Fig. 3) to generate a Hammett plot whose ρ-values reflect the negative charge developing on the leaving sulfur in the transition state.

Thiobenzamides were adopted as they best resemble the structure of the leaving group (Scheme 4).

Unfortunately only their pK_a in water[21] are available therefore it was necessary to make a correction for transfer from water to acetonitrile. It can be presumed that the change in Hammett ρ-values will be similar as in the case of benzoic acid whose ρ-values are 1 (by definition in water) and 2.64 in acetonitrile.[22]

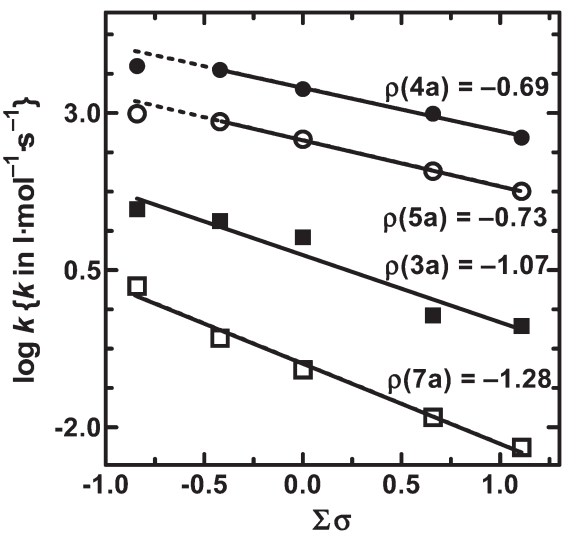


Fig. 1 Hammett plot for sulfurization of tris (subst. phenyl) phosphites (4-OCH_3, 4-CH_3, H, 4-Cl, 3-Cl) with **3a** (■), **4a** (●), **5a** (○) and **7a** (□).

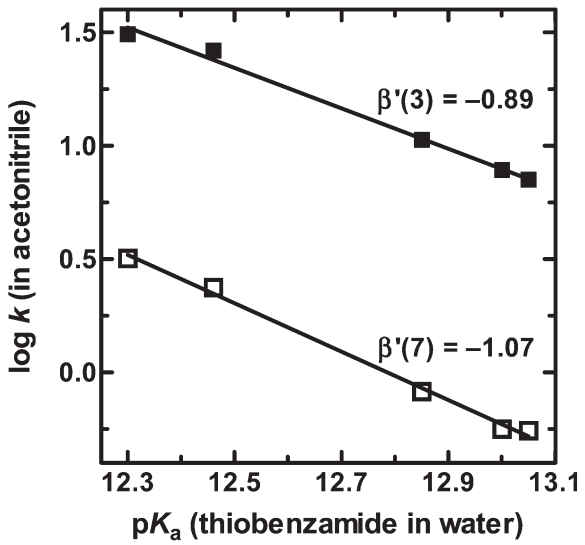


Fig. 2 Brønsted-type plot for sulfurization of triphenyl phosphite with **3a–e** (●) and **7a–e** (○) in acetonitrile at 25 °C.

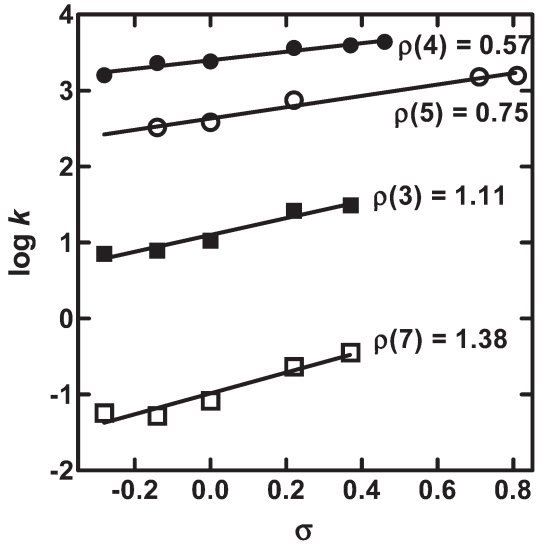
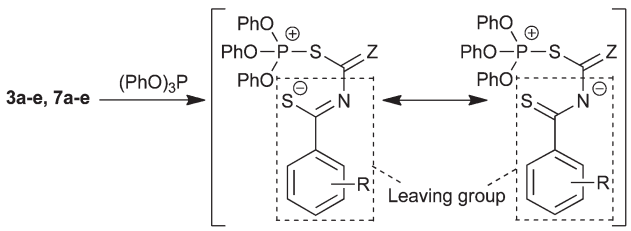


Fig. 3 Hammett plot for sulfurization of triphenyl phosphite with **3a–e** (■), **4a–f** (●), **5a–h** (○) and **7a–e** (□) in acetonitrile at 25 °C.



Scheme 4

When dividing the values of the slopes from Fig. 2 by 2.64 we obtained β_{lg}(**3a–e**) = −0.34 and β_{lg}(**7a–e**) = −0.40, respectively, which also correspond to early transition states. Unfortunately a similar Brønsted-type plot cannot be generated for **4a–f** and **5a, c,d,g,h** because the pK_a of the corresponding *O*-phenyl-thiocarbamates and *S*-phenyl-dithiocarbamates are not available.

The Hammett ρ-values for the reaction of triphenyl phosphite with **3a–e**, **4a–f**, **5a,c,d,g,h** and **7a–e** (Fig. 3) also indicate that there is a negative charge developing on the leaving sulfur. From their comparison it is clear that the relative negative charge seen by the substituents again decreases with increasing reactivity (*cf.* ρ-values 1.38 and 1.11 for related series **3a–e** and 7**a–e** or 0.75 and 0.57 for **4a–f** and **5a,c,d,g,h**). In the latter two series the lowering of ρ-values is not caused by a simple attenuation factor of the O and S bridging atom between the benzene ring and the 1,2,4-dithiazole because this factor is almost the same for both bridge atoms (f_O = 0.64 and f_S = 0.68).[23]

These Hammett ρ-values are only slightly dependent on solvent polarity for the most reactive dithiazoles **4a–f** but with the less reactive **5a,c,d,g,h** (and partially with **3a–e**, **7a–e**) the polar effects are more pronounced in a solvent of lower polarity (Table 2). Such an observation also supports the idea that the transition state for the most reactive 1,2,4-dithiazol-5-ones **4a–e** is looser than for the other less reactive dithiazoles.

In our previous paper[11b] we found that the ρ^- constants for the reaction of **8** with substituted triphenyl phosphites and phosphines had similar negative values (−1.1 and −0.86). Surprisingly, the substituent sensitivity was higher with phosphites although the oxygen bridge should attenuate transmission of the polar effects to a greater extent. Therefore we tried to carry out similar measurements with other 1,2,4-dithiazoles. Unfortunately, due to their high reactivity towards substituted triphenyl phosphines only the measurements (see ESI§) with the least reactive **7a** in acetonitrile were possible giving ρ = −1.63 which is a higher value than those observed for the substituted triphenyl phosphites (ρ = −1.28). However the observed attenuation factor of oxygen is much less than the common[23] value 0.64.

When the reaction of **7a** with triphenyl phosphine was studied triphasic kinetics were observed (Fig. 4).

During the first part of the kinetics the absorbance at 425 nm (which is the most intense absorption band of **7a**) decreased very quickly (reaction half-lives in milliseconds) and the observed rate constant was directly proportional to the triphenyl phosphine concentration but independent of added water. During the second phase of the kinetics the absorbance at 425 nm increased again but the observed rate constant was lower (half-lives in seconds) and was independent of both triphenyl phosphine as well as added water concentrations. The third reaction was somewhat slower (half-lives in tens of seconds) but its rate increased

Table 2 Hammett ρ-values measured in various solvents

	ρ (ACN)	ρ DCM	ρ (THF)	ρ (TOL)
3a–e	1.11 ± 0.15	1.31 ± 0.23	1.75 ± 0.06	1.34 ± 0.35
4a–f	0.57 ± 0.06	0.74 ± 0.06	0.74 ± 0.08	0.67 ± 0.07
5a–h	0.75 ± 0.07	1.14 ± 0.06	0.95 ± 0.06	1.31 ± 0.04
7a–e	1.38 ± 0.22	1.46 ± 0.31	1.19 ± 0.29	1.57 ± 0.26
(**7a–e**)[a]	(1.70 ± 0.10)	(1.86 ± 0.28)	(1.64 ± 0.10)	(1.95 ± 0.14)

[a] Without deviating point for **7b**.

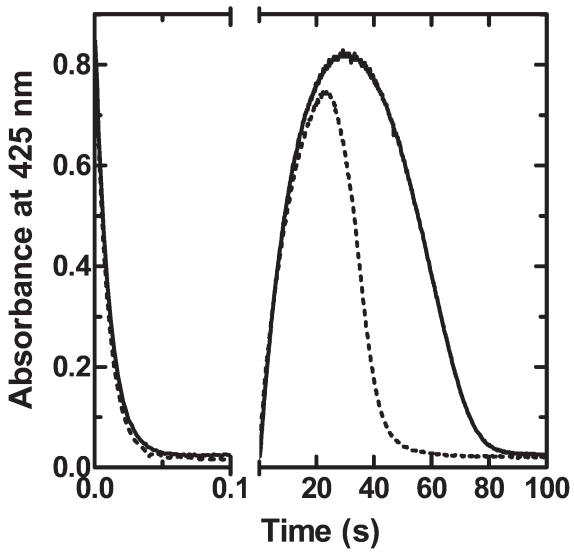


Fig. 4 Triphasic kinetics observed for the reaction of **3a** with triphenyl phosphine (0.01 mol l^{-1}) in dried ACN (solid line) and ACN containing 10 µl H_2O in 1 ml ACN *i.e.* 0.55 mol l^{-1} H_2O (dashed line).

with added water. This observation gives further evidence for the mechanism in Scheme 2. The first reaction corresponds to the formation (k_1) of a zwitterionic intermediate in Scheme 2 whereas the second one corresponds to the decomposition (k_2) of this intermediate to the triphenyl phosphine sulfide and thiobenzoyl isothiocyanate. The third phase then corresponds to the slow reaction of thiobenzoyl isothiocyanate with traces of water and its observed rate constant therefore steeply increases with added water. Similar biphasic kinetics confirming rapid buildup and slower decay of an intermediate was observed in the past for the reaction of diaryl disulfides with triphenyl phosphine.[15a] In the present study triphasic kinetics were only observed for the reaction of the least reactive **7a** and highly reactive triphenyl phosphine. In all other cases the kinetics involved only one or two phases; the rate of the first was always directly proportional to the P(III) compound concentration (see Table 1) and the second one corresponded to the slow water addition to the isocyanate/isothiocyanate by-product.

Treatment of our data by the dual substituent parameter approach introduced by *Taft* is also possible. For 1,2,4-dithiazole-5-ones **1–5** differing in substitution in position 3 the data measured in acetonitrile (with triphenyl phosphite) can be fitted using eqn (1) where $\rho_I\sigma_I$ and $\rho_R\sigma_R$ describe transmission of the inductive and resonance effects separately.

$$\log k = \log k^0 + \rho_I\sigma_I + \rho_R\sigma_R \qquad (1)$$

Using σ_I and σ_R from ref.[24] we obtained $\log k^0 = 0.19 \pm 0.08$, $\rho_I = 6.41 \pm 0.34$ and $\rho_R = -1.32 \pm 0.37$. As seen from the comparison of absolute ρ_I and ρ_R-values it is evident that the sulfurization is much more sensitive towards inductive effects. The transmission of mesomeric effects is less important which contradicts the aromatic (or pseudo-aromatic) character proposed for 1,2,4-dithiazole derivatives.[12,25] The π-orbital delocalization occurs only in the R–C═N–C═Z (Z = O, S) moiety (as seen from the elongation of the double bonds) and is not pronounced in the disulfide bridge.

The simultaneous attack at both sulfur atoms (biphilic mechanism) giving a pentavalent phosphorus intermediate or its equivalent involving back-donation[14c,16d] from sulfur S-2 to phosphorus can also be suggested to explain low ρ-values instead of nucleophilic attack at a single sulfur S-1. Such an explanation was suggested by Hall and Lloyd for the sulfurization of triphenyl phosphines, phosphonites and phosphinites with diaryl trisulfides and elemental sulfur (S_8). Hall and Lloyd found ρ-values constancy and an anomalous rate sequence for the sulfurization of P(III) compounds (*i.e.* $Ph_2POR > PhP(OR)_2 \gg PPh_3$ or $P(OR)_3$) whereas the normal[26] rate sequence (*i.e.* $PPh_3 > Ph_2POR > PhP(OR)_2 > P(OR)_3$) was observed for S_N2 attack by phosphorus at tetrahedral carbon. In the case of 1,2,4-dithiazole **7a** we also observed the same anomalous rate sequence in ACN at 25 °C. The second-order rate constants for the individual P(III) compounds were as follows: $k = 1.6 \times 10^5$ l mol^{-1} s^{-1} with methyl diphenylphosphinite, $k = 1.2 \times 10^5$ l mol^{-1} s^{-1} with dimethyl phenylphosphonite, $k = 1.06 \times 10^4$ l mol^{-1} s^{-1} with triphenyl phosphine and $k = 1.14 \times 10^3$ l mol^{-1} s^{-1} with trimethyl phosphite. The anomalous order of nucleophilicity could support the idea of back-donation[16d] from sulfur S-2 to phosphorus. Another explanation involves direct back-donation from sulfur S-1. It is well known[27] that in phosphate triesters [O═P(OR)$_3$], due to the difference in electronegativity of phosphorus (2.1) and oxygen (3.5), the P–O bonds are polarized toward oxygen ($P^{\delta+}$–$O^{\delta-}$–R). However, this activating effect is overshadowed by efficient back-donation of the lone electron pairs of the P–O–C bonds that lowers significantly the electrophilicity of the phosphorus centre in these compounds. The situation could be similar for the corresponding phosphorothioate (S═P(OR)$_3$) although this π-bonding is less effective in these thio analogues.

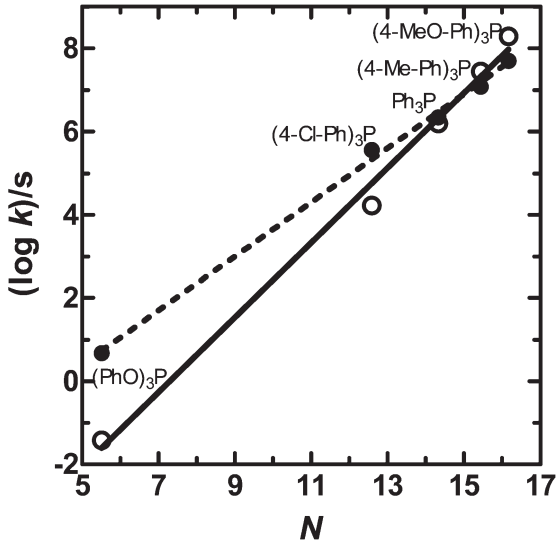
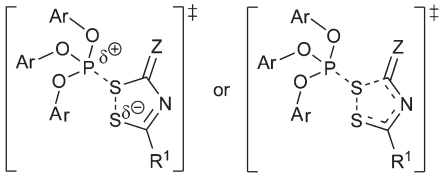


Fig. 5 Mayr plot for the sulfurization of triphenyl phosphite and substituted triphenyl phosphines with **7a** (○) and **8** (●). The dependence for **9** is not depicted in order to achieve better clarity because it is almost identical to those for **8**.

Phosphorous compounds are more powerfu1 nucleophiles than the corresponding amines[28] despite their weak basicity.[20] For some of them (*i.e.* for substituted phenyl phosphines and triphenyl phosphites) their nucleophilicity parameters N were recently published by Mayr and co-workers.[29] A good linear correlation of (log k)/s over a wide range of reactivities is observed for **7a**, **8** (Fig. 5) and **9**, showing that the nucleophilicity parameters N and s, which have been derived from reactions with benzhydrylium ions, are also relevant for S_N2 reaction of these nucleophiles at sulfur.

The slopes of the correlations shown in Fig. 5 do not equal 1 (they are from 0.62 to 0.89) as required by the Mayr equation,[30] indicating that the benzhydrylium-based nucleophile-specific parameters N and s can only be applied for such S_N2 reaction when an additional, electrophile-specific slope parameter s_E is added. Its value reflects less positive charge on sulfur S-1 in the transition state as compared with benzhydrylium cations where $s_E = 1$.

From all the above-mentioned observations an early transition state with little build-up of charge on phosphorus as well as on sulfur can be suggested. The extent of P–S bond formation and S–S bond cleavage is very similar in each of the reaction series but it gradually decreases with the reactivity of the 1,2,4-dithiazole derivatives. It also appears that the S–S bond breaking is somewhat advanced over P–S bond making in the transition state



Scheme 5

and this difference increases with increasing reactivity of both reactants. The following structures of the transition-state (Scheme 5) can be proposed:

The second apolar structure resembling a retro [4 + 1] cycloaddition is inspired by the published syntheses of various 1,2,4-dithiazoles from acyl isothiocyanates and phosphorus pentasulfide[31] or *N*,*N*-dimethylthiocarbamoyl isothiocyanate and elemental sulfur.[32] It is well known that the dependence of cycloaddition (and retro-cycloaddition[18]) rate constants on solvent polarity is a significant mechanistic criterion. The small solvent dependencies of Diels–Alder reactions and 1,3-dipolar cycloadditions signal minute charges of polarity during the activation process. These concerted cycloadditions also have early transition states.[33] Therefore the apolar transition state depicted in Scheme 5 should come into consideration when the reactivity of both phosphorus(III) compound as well as the 1,2,4-dithiazole derivative is high. On the other hand the transition state resembles the polar structure that may be more appropriate for the least reactive 1,2,4-dithiazoles.

Experimental

Synthesis

All the 1,2,4-dithiazoles **1–4** and **6–10** were synthesized and purified according to procedures published elsewhere.[7,8,12,31*a*,32,34] Synthesis of the new 3-[(subst.phenyl)thio]-1,2,4-dithiazole-5-ones (**5**) started from subst.phenyl dithiocarbamates prepared according to ref.[35]. Other chemicals were obtained from commercial suppliers and were used as received.

General method for the preparation of 5a,c,d,g,h

A solution of freshly prepared[35] subst.phenyl dithiocarbamate (6 mmol) in dry Et_2O (50 ml) was added dropwise over 30 min into a stirred and externally chilled (0–10 °C) solution of chlorocarbonylsulfenyl chloride (0.80 g, 6 mmol) in dry Et_2O (50 ml). The reaction mixture was stirred at 10 °C for 2 h. Solvent was evaporated at reduced pressure, and the residue was purified by recrystallization from a suitable solvent. See individual examples below:

5a: Yield 1.06 g (78%). M.p. 148–149 °C from ethyl acetate, ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.57 (m, 2H, Ar-$H_{3,5}$), 7.66 (m, 1H, Ar-H_4), 7.74 (m, 2H, Ar-$H_{2,6}$). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 124.2, 130.6, 132.7, 136.9, 183.6, 194.8. Anal. calcd for $C_8H_5NOS_3$: C, 42.27; H, 2.22; N, 6.16; S, 42.32. Found: C, 42.51; H, 2.24; N, 6.22; S, 42.41.

5c: Yield 1.18 g (82%). M.p. 129–130 °C from petrolether/diethyl ether, ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.61 (AA′XX′, 2H, Ar-$H_{2,6}$), 7.66 (AA′XX′, 2H, Ar-$H_{3,5}$), 2.47 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 21.6, 120.6, 131.4, 136.8, 143.7, 183.8, 195.5. Anal. calcd for $C_9H_7NOS_3$: C, 44.79; H, 2.92; N, 5.80; S, 39.86. Found: C, 44.96; H, 2.90; N, 5.80; S, 40.01.

5d: Yield 1.14 g (73%). M.p. 163–164 °C from ethyl acetate, ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.69 (AA′XX′, 2H, Ar-$H_{2,6}$), 7.56 (AA′XX′, 2H, Ar-$H_{3,5}$). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 122.6, 131.0, 138.1, 139.7, 183.4, 193.8. Anal. calcd for $C_8H_4ClNOS_3$: C, 36.71; H, 1.54; Cl, 13.54; N, 5.35; S, 36.75. Found: C, 36.93; H, 1.55; Cl, 13.27; N, 5.27; S, 36.99.

5g: Yield 1.08 g (66%). M.p. 182–184 °C from diethyl ether, ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.62 (t, 1H, J = 2.0 Hz, Ar-H_2), 8.50 (ddd, 1H, J = 8.4 and 2.3 and 1.0 Hz, Ar-H_4), 8.09 (ddd, 1H, J = 7.7 and 1.8 and 1.0 Hz, Ar-H_6), 7.80 (t, 1H, J = 8.0, Ar-H_5). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 126.9, 127.2, 131.3, 131.4, 142.3, 149.0, 182.8, 191.5. Anal. calcd for $C_8H_4N_2O_3S_3$: C, 35.28; H, 1.48; N, 10.29; S, 35.32. Found: C, 35.56; H, 1.52; N, 10.03; S, 35.38.

5h: Yield 0.98 g (60%). M.p. 136–138 °C from ethyl acetate, ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.39 (AA′XX′, 2H, Ar-$H_{3,5}$), 7.96 (AA′XX′, 2H, Ar-$H_{2,6}$). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 125.1, 132.3, 137.3, 150.0, 182.7, 191.0. Anal. calcd for $C_8H_4N_2O_3S_3$: C, 35.28; H, 1.48; N, 10.29; S, 35.32. Found: C 35.31, H 1.44, N 10.27, S 35.37.

Kinetic measurements

The kinetic measurements were carried out on a Diode Array Stopped-Flow SX.18 MV-R (Applied Photophysics) spectrophotometer or on a Hewlett Packard HP 8453 Diode Array at 25 °C under pseudo-first order conditions. The observed pseudo-first order rate constants k_{obs} were calculated from the measured time dependence of absorbance at a suitable wavelength with the help of an optimization program. Solvents used for kinetic measurements were of HPLC quality and were dried and distilled under argon prior to use. Due to potential oxidation of phosphorus(III) compounds all the solutions were freshly prepared just before kinetic measurements.

NMR experiments

^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker Avance 3 400 MHz instrument. Chemical shifts δ are referenced to solvent residual peaks δ(DMSO-d_6) = 2.50 (^{1}H) and 39.6 ppm (^{13}C), and δ($CDCl_3$) = 7.27 (^{1}H) and 77.0 (^{13}C). ^{31}P NMR shifts are referenced to 85% phosphoric acid (external standard).

Reaction of PADS, TETD and Beaucage's reagent with triethyl or triphenyl phosphite (^{31}P NMR kinetic study)

Sulfurizing reagent (0.1 mmol) was dissolved in 0.5 ml of $CDCl_3$ or CD_3CN and the corresponding phosphite (0.1 mmol) in 0.5 ml of $CDCl_3$ or CD_3CN was added so that the initial concentration of both components was 0.1 mol l^{-1}. Then ^{31}P NMR spectra were recorded after appropriate intervals (from minutes to hours). The spectrum always contained two singlets belonging to triphenyl phosphorothioate (δ_P = 55.2 ppm in CD_3CN[36*a*] and

53.7 ppm in $CDCl_3$ [36b]) or triethyl phosphorothioate (δ_P = 68.5 ppm in CD_3CN[36a] and 67.2 ppm in $CDCl_3$ [36c]) and triphenyl phosphite (δ_P = 129.7–130 ppm in CD_3CN[36a,d] and 127.9 ppm in $CDCl_3$ [36e]) or triethyl phosphite (δ_P = 139.9 ppm in CD_3CN[36a] and 137.5 in $CDCl_3$ [36f]), whose ratio was changing with time. From integrals the kinetic curve was constructed and the second-order rate constant was calculated.

Trapping experiments

3-Ethoxy-1,2,4-dithiazole-5-one (**1**) (0.53 g, 3.25 mmol) was dissolved in 20 ml of acetonitrile under an argon atmosphere at 20 °C and a solution containing triphenyl phosphite (1.0 g, 3.25 mmol) in 5 ml of acetonitrile was added in one portion. The reaction mixture was stirred for 1 min and then 4-methoxyaniline (0.40 g, 3.25 mmol) in 5 ml of acetonitrile was added. After 1 h the reaction mixture was filtered and white crystalline *O*-ethyl *N*-[(4-methoxyphenyl)carbamoyl]thiocarbamate (**11**, 0.60 g) was collected. Acetonitrile was recovered from the filtrate and the semi-solid residue was chromatographed on a silica gel (ethyl acetate–hexane 1 : 4) to obtain a further portion of **11** (0.20 g). The chromatographic column was then washed with methanol to obtain 0.99 g (89%) of triphenyl phosphorothioate. The overall yield of **11** was 0.80 g (96%). M.p. 145–146 °C, ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.41 (t, J = 7.2, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.49 (q, J = 7.2, 2H, OCH_2), 6.87 (AA′XX′, 2H, Ar-$H_{3,5}$), 7.46 (AA′XX′, 2H, Ar-$H_{2,6}$), 9.47 (bs, 1H, NH), 11.26 (bs, 1H, NH). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 13.7 (CH_3), 55.4 (OCH_3), 67.2 (OCH_2), 114.1 (Ar-$C_{3,5}$), 121.9 (Ar-$C_{2,6}$), 129.9 (Ar-C_1), 150.5 (C═O), 156.5 (Ar-C_4), 188.0 (C═S). Elemental analysis: found C, 52.11; H, 5.58; N, 11.10; S, 12.74. $C_{11}H_{14}N_2O_3S$ requires C, 51.95; H, 5.55; N, 11.02; S, 12.61.

3-Phenoxy-1,2,4-dithiazole-5-one (**4a**) (0.5 g, 2.36 mmol) was dissolved in 10 ml of acetonitrile under an argon atmosphere at 20 °C and a solution containing triphenyl phosphite (0.73 g, 2.36 mmol) in 5 ml of acetonitrile was added in one portion. The reaction mixture was stirred for 1 min and then 4-methoxyaniline (0.29 g, 2.36 mmol) in 5 ml of acetonitrile was added. After 1 h the reaction mixture was filtered and white crystalline *O*-phenyl *N*-[(4-methoxyphenyl)carbamoyl]thiocarbamate (**12**, 0.35 g) was collected. Acetonitrile was removed from the filtrate and the semi-solid residue was chromatographed on silica gel (ethyl acetate–hexane 1 : 9) to obtain a further portion of **12** (0.30 g). The chromatographic column was then washed with methanol to obtain 0.72 g (90%) of triphenyl phosphorothioate. The overall yield of **12** was 0.65 g (84%). M.p. 144–147 °C, ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.77 (s, 3H, OCH_3), 6.85 (AA′XX′, 2H, Ar-$H_{3,5}$), 7.10 (d, J 7.6, 2H, Ar-$H_{2,6}$), 7.33 (t, J = 7.6, 1H, Ar-H_4), 7.46 (m, 4H, AA′XX′ + Ar-$H_{3,5}$), 9.84 (bs, 1H, NH), 11.22 (bs, 1H, NH). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.4, 114.2, 122.1, 122.5, 126.9, 129.5, 129.5, 150.3, 151.8, 156.7, 188.0. One C_{quart} is missing in the spectrum in $CDCl_3$ because two peaks in the aromatic region have exactly the same chemical shift. In DMSO-d_6 δ 3.73 (s, 3H, OCH_3), 6.92 (AA′XX′, 2H, Ar-$H_{3,5}$), 7.16 (d, J = 7.6, 2H, Ar-$H_{2,6}$), 7.31 (t, J = 7.6, 1H, Ar-H_4), 7.45 (m, 4H, AA′XX′ + Ar-3,5), 10.26 (bs, 1H, NH), 11.81 (bs, 1H, NH). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 55.3, 114.3, 121.3, 122.7, 126.6, 129.7, 130.6, 148.9, 152.5, 155.9, 188.3. Elemental analysis: found C, 59.47; H, 4.59; N, 9.32; S, 10.68. $C_{15}H_{14}N_2O_3S$ requires C, 59.59; H, 4.67; N, 9.27; S, 10.61.

3-Phenylthio-1,2,4-dithiazole-5-one (**5a**) (0.5 g, 2.2 mmol) was dissolved in 75 ml of acetonitrile under an argon atmosphere at 20 °C and a solution containing triphenyl phosphite (0.68 g, 2.2 mmol) in 25 ml of acetonitrile was added in one portion. The reaction mixture was stirred for 5 s and then aniline (0.20 g, 2.2 mmol) in 25 ml of acetonitrile was added. After 2 h the acetonitrile was evaporated and the semi-solid residue was chromatographed on a silica (dichloromethane–pentane 1 : 1) to obtain 0.60 g (94%) of yellowish crystals **13** with m.p. 181–182 °C. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 7.11 (m, 1H, Ar-H), 7.36 (m, 2H, Ar-H), 7.44–7.53 (m, 7H, Ar-H), 9.45 (bs, 1H, NH), 11.61 (bs, 1H, NH). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ 119.2, 123.9, 129.2, 129.5, 130.3, 131.4, 136.3, 137.8, 149.5, 202.8. Elemental analysis: found C, 58.51; H, 4.12; N, 9.59; S, 22.34. $C_{14}H_{12}N_2OS_2$ requires C, 58.31; H, 4.19; N, 9.71; S, 22.24.

Conclusions

3-Substituted-1,2,4-dithiazole-5-ones and 5-thiones were found to be stable and extraordinarily efficient sulfurizing agents of phosphorus(III) compounds. Their reactivity is as much as six orders of magnitude higher (especially with our original 3-phenoxy and 3-phenylthio-1,2,4-dithiazole-5-ones) than for commercially available sulfurizing agents like for example Beaucage's agent or phenylacetyldisulfide (PADS). Moreover their reactivity is virtually independent of solvent polarity which makes 1,2,4-dithiazoles to be promising sulfurizing agents in automated synthesis of phosphorothioate oligoribonucleotides. In order to understand the sulfurization reaction the detailed reaction mechanism was also studied. It was found that the insensitivity of the reaction rate towards solvent polarity is probably caused by some kind of electron back donation from sulfur to phosphorus in the transition state of the reaction.

Notes and references

1 (*a*) F. Eckstein and G. Gish, *Trends Biochem. Sci.*, 1989, **14**, 97–100; (*b*) G. Zon and W. J. Stec, in *Oligonucleotides and Analogues: A Practical Approach*, ed. F. Eckstein, IRL Press, Oxford, 1991, pp. 87–108; (*c*) P. Iversen, *Anti-Cancer Drug Des.*, 1991, **6**, 539–568; (*d*) P. C. Zamecnik, in *Prospects for Antisense Nucleic Acid Therapy for Cancer and AIDS*, ed. E. Wickstrom, Wiley Liss, New York, 1991, pp. 1–6; (*e*) S. Agrawal, *Trends Biotechnol.*, 1992, **10**, 152; (*f*) C. K. Mirabelli and S. T. Crooke, in *Antisense Research and Applications*, ed. S. T. Crooke and B. Lebleu, CRC, Ann Arbor, 1993, pp. 7–35 and references cited therein; (*g*) N. D. Sinha, S. N. Kuchimanchi, G. Miranda and S. Shaikh, *Indian J. Chem.*, 2006, **45B**, 2297–2304; (*h*) C. Höbartner and F. Wachowius, in *The Chemical Biology of Nucleic Acids*, ed. G. Mayer, J. Wiley & Sons, Ltd., Chippenham, 2010, p. 19.
2 (*a*) Q. Xu, K. Musier-Forsyth, R. P. Hammer and G. Barany, *Nucleic Acids Res.*, 1996, **24**, 1602–1607; (*b*) Q. Xu, G. Barany, R. P. Hammer and K. Musier-Forsyth, *Nucleic Acids Res.*, 1996, **24**, 3643–3644; (*c*) Z. Zhang, A. Nichols, J. X. Tang, Y. Han and J.-Y. Tang, *Tetrahedron Lett.*, 1999, **40**, 2095–2098; (*d*) J.-Y. Tang, Z. Han, J. X. Tang and Z. Zhang, *Org. Process Res. Dev.*, 2000, **4**, 194–198; (*e*) Z. Zhang, Y. Han, J. X. Tang and J.-Y. Tang, *Tetrahedron Lett.*, 2002, **43**, 4347–4349; (*f*) A. P. Guzaev, *Tetrahedron Lett.*, 2011, **52**, 434–437.
3 (*a*) P. C. J. Kamer, H. C. P. F. Roelen, H. van den Elst, G. A. van der Marel and J. H. van Boom, *Tetrahedron Lett.*, 1989, **30**, 6757–6760;

(*b*) R. P. Iyer, L. R. Phillips, W. Egan, J. B. Regan and S. L. Beaucage, *J. Org. Chem.*, 1990, **55**, 4693–4699; (*c*) H. Vu and B. L. Hirschbein, *Tetrahedron Lett.*, 1991, **32**, 3005–3008; (*d*) M. V. Rao, C. B. Reese and Z. Zhao, *Tetrahedron Lett.*, 1992, **33**, 4839–4842; (*e*) W. J. Stec, B. Uznanski and A. Wilk, *Tetrahedron Lett.*, 1993, **34**, 5317–5320; (*f*) M. V. Rao and K. Macfarlane, *Tetrahedron Lett.*, 1994, **35**, 6741–6744; (*g*) V. A. Efimov, A. L. Kalinkina, O. G. Chakhmakhcheva, T. S. Hill and K. Jayaraman, *Nucleic Acids Res.*, 1995, **23**, 4029–4033; (*h*) Z. Zhang, A. Nichols, M. Alsbeti, J. X. Tang and J.-Y. Tang, *Tetrahedron Lett.*, 1998, **39**, 2467–2470; (*i*) A. H. Krotz, A. Hang, D. Gorman and A. N. Scozzari, *Nucleosides, Nucleotides Nucleic Acids*, 2005, **24**, 1293–1299; (*j*) Z. Wang, Q. Song and Y. S. Sanghvi, in *Methods in Molecular Biology, vol. 288: Oligonucleotide Synthesis: Methods and Applications*, ed. P. Herdewijn, Humana Press Inc., Totowa, New Jersey, 2005.

4 (*a*) J. A. Mukhlall and W. Hersh, *Nucleosides, Nucleotides Nucleic Acids*, 2011, **30**, 706–725; (*b*) J. A. Mukhlall, B. C. Noll and W. Hersh, *J. Sulfur Chem.*, 2011, **32**, 199–212.

5 Z. Zhang, A. Nichols, J. X. Tang, M. Alsbeti and J.-Y. Tang, *Nucleosides Nucleotides*, 1997, **16**, 1585–1588.

6 Z. S. Cheruvallath, R. L. Carty, M. N. Moore, D. C. Capaldi, A. H. Krotz, P. D. Wheeler, B. J. Turney, S. R. Craig, H. J. Gaus, A. N. Scozzari, D. L. Cole and V. T. Ravikumar, *Org. Process Res. Dev.*, 2000, **4**, 199–204.

7 J. Goerdeler and K. Nandi, *Chem. Ber.*, 1981, **114**, 549–563.

8 J. Goerdeler and K. Nandi, *Chem. Ber.*, 1975, **108**, 3066–3070.

9 (*a*) J. Goerdeler and W. Teller, *Tetrahedron Lett.*, 1972, **16**, 1513–1514; (*b*) D. J. Cane-Honeysett, M. D. Dowle and M. E. Wood, *Synlett*, 2000, 1622–1624.

10 (*a*) W. M. Abdou, I. T. Hennawy and Y. O. El Khoshnieh, *J. Chem. Res. (M)*, 1995, 442–451; (*b*) W. M. Abdou, I. T. Hennawy and Y. O. El Khoshnieh, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1996, **109–110**, 557–560.

11 (*a*) J. Hanusek, M. A. Russel, A. P. Laws and M. I. Page, *Tetrahedron Lett.*, 2007, **48**, 417–419; (*b*) J. Hanusek, M. A. Russell, A. P. Laws, P. Jansa, J. H. Atherton, K. Fettes and M. I. Page, *Org. Biomol. Chem.*, 2007, **5**, 478–484.

12 L. Chen, T. R. Thompson, R. P. Hammer and G. Barany, *J. Org. Chem.*, 1996, **61**, 6639–6645.

13 (*a*) J. Goerdeler and A. Schulze, *Chem. Ber.*, 1982, **115**, 1252–1255; (*b*) J. Goerdeler and K. Jonas, *Chem. Ber.*, 1966, **99**, 3572–3581.

14 (*a*) P. D. Bartlett and G. Meguerian, *J. Am. Chem. Soc.*, 1956, **78**, 3710–3715; (*b*) P. D. Bartlett, E. F. Cox and R. E. Davis, *J. Am. Chem. Soc.*, 1961, **83**, 103–109; (*c*) J. R. Lloyd, N. Lowther, G. Zsabo and C. D. Hall, *J. Chem. Soc., Perkin Trans. 2*, 1985, 1813–1817.

15 (*a*) L. E. Overman, D. Matzinger, E. M. O'Connor and J. D. Overman, *J. Am. Chem. Soc.*, 1974, **96**, 6081–6089; (*b*) L. E. Overman and S. T. Petty, *J. Org. Chem.*, 1975, **40**, 2779–2782; (*c*) L. E. Overman and E. M. O'Connor, *J. Am. Chem. Soc.*, 1976, **98**, 771–775.

16 (*a*) F. Fehér and D. Kurz, *Naturforschg. B*, 1968, **23**, 1030–1033; (*b*) D. N. Harpp and R. A. Smith, *J. Org. Chem.*, 1979, **44**, 4140–4144; (*c*) D. N. Harpp, D. K. Ash and R. A. Smith, *J. Org. Chem.*, 1980, **45**, 5155–5160; (*d*) C. D. Hall, B. R. Tweedy, R. Kayhanian and J. R. Lloyd, *J. Chem. Soc., Perkin Trans. 2*, 1992, 775–779.

17 C. G. Moore and B. R. Trego, *Tetrahedron*, 1962, **18**, 205–218.

18 D. B. Denney and M. J. Boskin, *J. Am. Chem. Soc.*, 1960, **82**, 4736–4738.

19 (*a*) D. J. Mclennan, *Tetrahedron*, 1978, **34**, 2331–2341; (*b*) M. Page and A. Williams, in *Organic & Bio-organic Mechanisms*, Addison Wesley Longman Ltd., Singapore, 1997.

20 W. A. Henderson Jr. and C. A. Streuli, *J. Am. Chem. Soc.*, 1960, **82**, 5791–5794.

21 (*a*) W. Walter and R. F. Becker, *Justus Liebigs Ann. Chem.*, 1969, **727**, 71–80; (*b*) K. Waisser, M. Čeladník, R. Karlíček and K. Palát, *Cesk. Farm.*, 1978, **27**, 326–327.

22 L. M. Yagupolskii, V. N. Petrik, N. V. Kondratenko, L. Sooväli, I. Kaljurand, I. Leito and I. A. Koppel, *J. Chem. Soc., Perkin Trans. 2*, 2002, 1950–1955.

23 A. Williams, *Free Energy Relationships in Organic and Bio-organic Chemistry*, RSC, Cambridge, 2003.

24 C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165–195.

25 (*a*) M. P. Sammes, in *Comprehensive Heterocyclic Chemistry I*, ed. A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984, ch. 4.34, vol. 6, p. 903; (*b*) G. Barany, *Cryst. Struct. Commun.*, 1982, **11**, 913–928.

26 (*a*) D. Aksnes and G. Aksnes, *Acta Chem. Scand.*, 1964, **18**, 38–46; (*b*) J. Songstad and T. Thorstenson, *Acta Chem. Scand., Ser. A*, 1976, **30**, 724–730.

27 D. G. Gilheany, *Chem. Rev.*, 1994, **94**, 1339–1374.

28 (*a*) W. A. Henderson Jr. and S. A. Buckler, *J. Am. Chem. Soc.*, 1960, **82**, 5794–5800; (*b*) H. R. Hudson, in *The Chemistry of Organophosphorus Compounds I*, ed. F. Hartley, *The Chemistry of Functional Groups*, series ed. S. Patai, J. Wiley&Sons, Chichester, 1990, ch. 11–12, pp. 385–487.

29 B. Kempf and H. Mayr, *Chem.–Eur. J.*, 2005, **29**, 917–927.

30 (*a*) H. Mayr and M. Patz, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 938–957; (*b*) H. Mayr and A. R. Ofial, *J. Phys. Org. Chem.*, 2008, **21**, 584–595; (*c*) T. Kanzian, T. A. Nigst, A. Maier, S. Pichl and H. Mayr, *Eur. J. Org. Chem.*, 2009, 6379–6385.

31 (*a*) J.-L. Derocque and J. Vialle, *Bull. Soc. Chim. Fr.*, 1966, 1183–1186; (*b*) J. W. MacDonald and D. M. McKinnon, *Can. J. Chem.*, 1967, **45**, 1225–1229.

32 J. E. Oliver, R. T. Brown and N. L. Redfearn, *J. Heterocycl. Chem.*, 1972, **9**, 447–449.

33 R. Huisgen, *Pure Appl. Chem.*, 1980, **52**, 2283–2302.

34 (*a*) M. E. Wood, D. J. Cane-Honeysett, M. D. Dowle, S. J. Coles and M. B. Hursthouse, *Org. Biomol. Chem.*, 2003, **1**, 3015–3023; (*b*) R. Seltzer and W. J. Cousidine, *J. Org. Chem.*, 1970, **35**, 1665–1666; (*c*) O. Ponomarov, Z. Padělková and J. Hanusek, *J. Heterocycl. Chem.*, 2011, **48**, 1225–1228; (*d*) R. Gerner and G. Gattow, *Z. Anorg. Allg. Chem.*, 1985, **525**, 112–120.

35 N. A. Meinhardt, S. Z. Cardon and P. W. Vogel, *J. Org. Chem.*, 1960, **25**, 1991–1992.

36 (*a*) A. H. Krotz, S. Hang, D. Gorman and A. N. Scozzari, *Nucleosides, Nucleotides Nucleic Acids*, 2005, **24**, 1293–1299; (*b*) J. Hernandez, F. M. Goycoolea, D. Zepeda-Rivera, J. Juarez-Onofre, K. Martinez, J. Lizardi, M. Salas-Reyes, B. Gordillo, C. Velazquez-Contreras, O. Garcia-Barradas, S. Cruz-Sanchez and Z. Dominguez, *Tetrahedron*, 2006, **62**, 2520–2528; (*c*) J. Heliński, Z. Skrzypczyński, J. Wasiak and J. Michalski, *Tetrahedron Lett.*, 1990, **31**, 1557–1558; (*d*) A. Kers, I. Kers, J. Stawinski, M. Sobkowski and A. Kraszewski, *Tetrahedron*, 1996, **52**, 9931–9944; (*e*) H.-J. van Manen, K. Nakashima, S. Shinkai, H. Kooijman, A. L. Spek, F. C. J. M. van Veggel and D. N. Reinhoudt, *Eur. J. Inorg. Chem.*, 2000, 2533–2540; (*f*) G. Ilia, S. Iliescu, L. Macarie and A. Popa, *Heteroat. Chem.*, 2008, **19**, 360–364.

