JOC The Journal of Organic Chemistry

ARTICLE

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Thionations Using a P_4S_{10}–Pyridine Complex in Solvents Such as Acetonitrile and Dimethyl Sulfone

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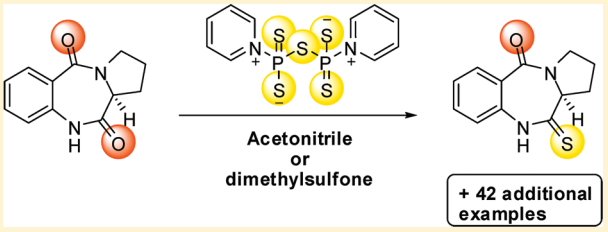
Supporting Information

ABSTRACT: Tetraphosphorus decasulfide (P_4S_{10}) in pyridine has been used as a thionating agent for a long period of time. The moisture-sensitive reagent has now been isolated in crystalline form, and the detailed structure has been determined by X-ray crystallography. The thionating power of this storable reagent has been studied and transferred to solvents such as acetonitrile in which it has proven to be synthetically useful and exceptionally selective. Its properties have been compared with the so-called Lawesson reagent (LR). Particularly interesting are the results from thionations at relatively high temperatures (~165 °C) in dimethyl sulfone as solvent. Under these conditions, for instance, acridone and 3-acetylindole could quickly be transformed to the corresponding thionated derivatives. Glycylglycine similarly gave piperazinedithione. At these temperatures, LR is inefficient due to rapid decomposition. The thionated products are generally cleaner and more easy to obtain because in the crystalline reagent, impurities which invariably are present in the conventional reagents, P_4S_{10} in pyridine or LR, have been removed.



INTRODUCTION

In spite of the fact that the combination of P_4S_{10} **1** and pyridine, as a successful reagent for thionation of amides and several other classes of molecules was introduced by Klingsberg[1] as early as in 1951, the so-called Lawesson's reagent (**2a**, LR) has been much more commonly used for this purpose (Figure 1).[2−8] Actually, the reagent **2a** was introduced in 1968 for transformations in organic chemistry by Schumacher,[2] who utilized it with a considerable number of reactants, such as benzophenone, triphenylphosphine oxide, and camphor, which were thionated in fair yields, but also interactions with more unexpected reactants like aziridine and phenylacetylene were studied. Unfortunately, Schumacher's seminal work has only partially been considered in the reviews dealing with **2a** by Cava,[4] Jesberger,[5] Woollins,[9] Kaushik,[10] and Ozturk[6] et al.

Pyridine and P_4S_{10} react readily to form the zwitterionic, nonsmelling reagent (**3**), whose composition, $P_2S_5 \cdot 2C_5H_5N$, was studied as early as 1967−1968 by German inorganic chemists[8,11] who obtained evidence for structure **3** by ^{31}P NMR data[12] as well as by comparison with related molecules. In spite of that, Weintraub[13] and Söder,[13,14] obviously without knowledge of the previous work, much later introduced structure **4** for the product obtained from P_4S_{10} and pyridine. This composition, $P_4S_{10} \cdot 4C_5H_5N$, has been retained even in relatively recent work.[15] A large number of other methods to modify P_4S_{10} are known, such as addition of $NaHCO_3$ or Na_2CO_3, R-Li, and $(TMS)_2O$ and, as recently demonstrated, even silicon oil.[16−23] Some of these procedures are difficult to reproduce.[24]

We became intrigued by the overwhelming bias in favor of **2a** over **3** when we found that indigo **5** (Figure 2) reacted efficiently

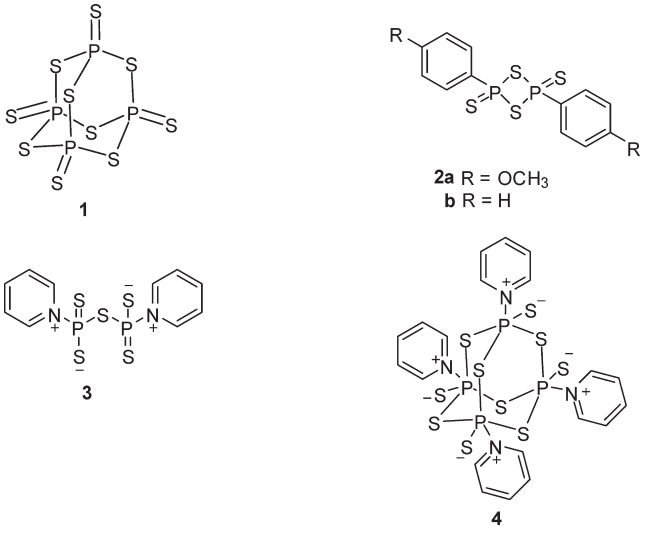


Figure 1. Graphical representation of molecular structures **1**−**4**.

with **3** to give **6** in refluxing pyridine, whereas **2a** was totally inefficient in this solvent.[25] It should be noted though that **2a** and related reagents (e.g., **2b**) will react with pyridine to give, e.g., **8**.[26,27] At an early phase in this project, it was noted that the reagent **3** has a much higher thermal stability than **2a**. It has even been reported that **2a** will start to decompose above 110 °C,[5,6]

Received: September 27, 2010
Published: February 22, 2011

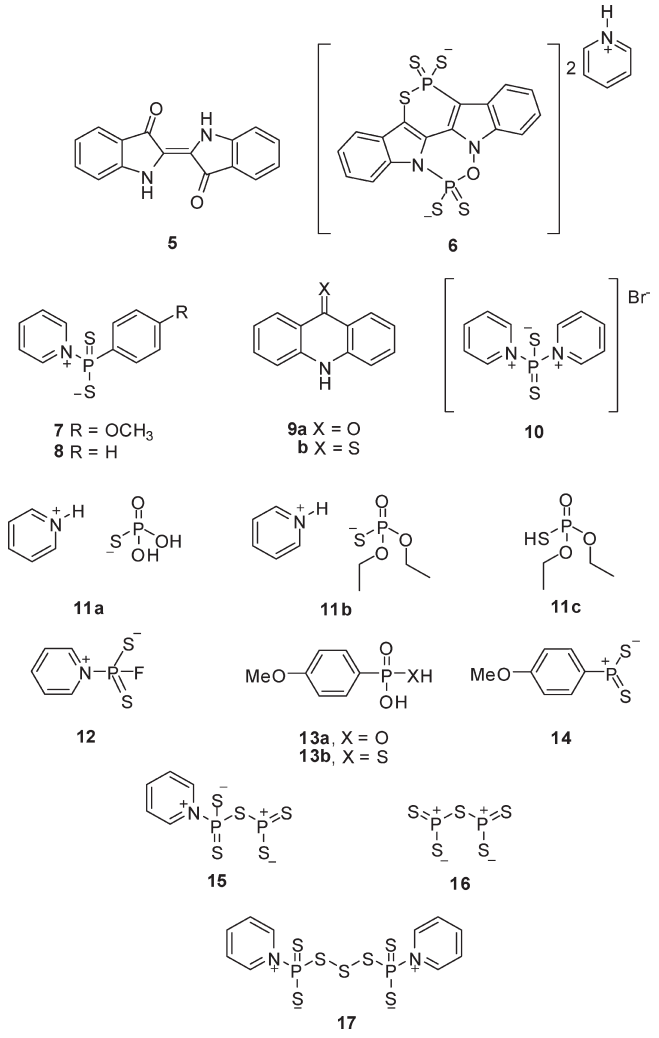


Figure 2. Graphical representation of molecular structures **5**−**17**.

whereas the zwitterionic molecule **3** can be successfully used for thionations as a melt or, even better, dissolved in dimethylsulfone, in the range 165−175 °C (vide infra).

There are further drawbacks with the reagent **2a**; thus it has been reported that acridone **9a** can be converted to the corresponding thionated molecule **9b** by P_4S_{10} in HMPA, whereas the reagent **2a** failed.[28] It has now been found that **9a** is readily (1 h at reflux) thionated by **3** in acetonitrile or within minutes in hot dimethyl sulfone. Additional drawbacks with the reagent **2a** are its low solubility, the coformation of foul-smelling side products that are difficult to separate from the desired molecules[28−30] (column chromatography is often required), and that HMPA (a solvent that is prohibited in Sweden and many other countries) quite often has to be used. The low solubility of **2a** has induced workers to introduce various variants such as fluorous LR reagents[31] and LR reagents carrying additional substituents.[21] The low solubility has induced several research groups to use LR in combination with microwaves.[32,33] In this fashion, γ-lactones can be converted to γ-thiolactones, for example.[32] Actually, the drawbacks associated with **2a** have prompted Ley et al. to develop a polymer-supported thionating reagent prepared from a diamine resin and ethyl dichlorothiophosphate.[29] Finally, it should be stressed that in none of the thionations described herein chromatographic purification was necessary.

RESULTS AND DISCUSSION

With this background, we decided to study in more detail the efficiency of **3** as a thionating agent with special emphasis on the utilization of the reagent in "neutral" solvents such as acetonitrile for the preparation of thioamides, a class of compounds that are of importance as they can be readily converted to several types of heterocycles[30] and also coupled with arylboronic acids under Pd catalysis.[34−37] Thus, e.g., pyridine-2(1*H*)-thione will undergo carbon−carbon cross-coupling with phenylboronic acid in high yield to give 2-phenylpyridine.[34−37] Similarly, 2-thiouracil has been coupled with, e.g., 2-furyltributylstannane to 2-furyl-2-pyrimidin-4-one.[38]

As two structures have been suggested for the P_4S_{10}−pyridine reagent we have also performed an X-ray study, which gave conclusive evidence for structure **3**. A somewhat related structure, namely **10**, has been determined by Meisel et al. (Figure 2).[39] This ionic complex seems not to have been used for thionation purposes. This is also true for the hybrides **7** and **8**.

The zwitterionic reagent **3** has fair solubility in hot acetonitrile and a good solubility in hot pyridine. Addition of water to a hot solution/suspension of **3** in acetonitrile will quickly result in a clear solution. Actually, the reagent quickly undergoes extensive degradation in the presence of water; big, beautiful crystals of the salt **11a** could be isolated and the detailed structure determined by X-ray crystallography. The salt **11a** is readily soluble in water and had previously been prepared and studied by reaction of the fluorine-containing zwitterionic pyridinium salt **12** (Figure 2) with ethyldiphenylphosphine.[40,41] The ready formation and high solubility of the salt **11a** can be advantageously used during workup of, e.g., thioamides. Thus, in a typical experiment, 4 equiv of an amide was heated with 1.1 equiv of the reagent **3** in dry acetonitrile, and in connection with the workup any remaining reagent was readily removed by addition of water. The reagent **3** will also decompose when treated with alcohols. Thus, ethanol gave the salt **11b**. The structure of **11b** was proven by neutralizing the strong (pK_a = 1.62)[42] acid **11c** with pyridine, which gave an identical product (Figure 2). The acid **11c** was readily prepared by dissolution of P_4S_{10} in ethanol. The reagent **2a** (LR) is also sensitive to water, as noted already in 1956 by Lecher et al. who found that after a period of reflux (18 h) in water, the reagent was completely converted to *p*-anisylphosphoric acid **13a**.[43] The same molecule had in 2002 also been synthesized by Aragoni et al. by first heating **2a** together with an excess of methyl iodide at reflux for 5 h.[44] This methylated intermediate thus obtained, was then stored for two weeks in open atmosphere which gave *p*-anisylphosphoric acid **13a** suitable for X-ray studies. The same molecule **13a** has now been obtained quite quickly after a period of reflux (5 min) of **2a** in acetonitrile containing a few percent of water. The partially hydrolyzed molecule **13b**, which can readily undergo cyclocondensation, was never observed.[45] It thus appears that the reagent **2a** is much more sensitive to water than previously believed. The quick hydrolysis observed in this medium can be perceived by assuming that dedimerization in acetonitrile to the reactive species **14** is particularly favorable in this medium with its high dielectric constant. Actually, there is evidence[42,46−50] that the reagent **2a** dissociates to the reactive species **14** in a rate-determining step during the thionation process. It is at present not clear if the reagent **3** thionates as such or via dissociation to species such as **15** or **16**. Formation of **16** has previously been formulated as part of the dissociation of P_4S_{10}.[6]

dx.doi.org/10.1021/jo101865y |*J. Org. Chem.* 2011, 76, 1546–1553

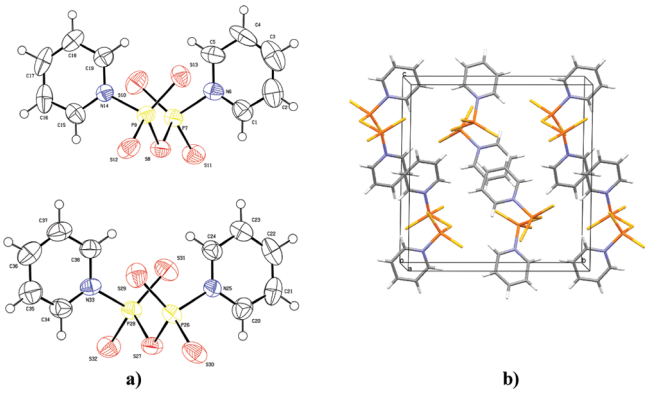


Figure 3. (a) Molecular and (b) crystal structure of **3**. The crystal structure contains two symmetry independent molecules (a).

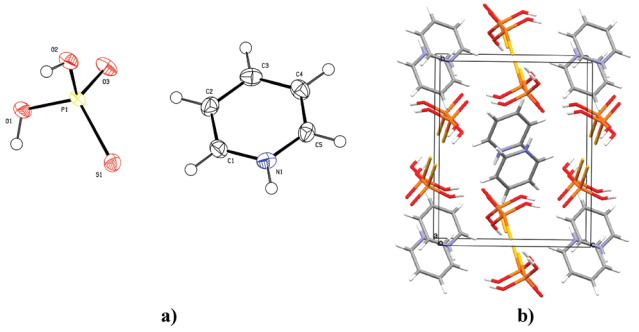


Figure 4. (a) Molecular and (b) crystal structure of **11a**.

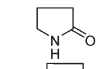
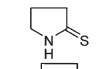
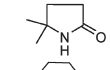
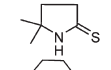
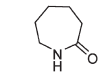
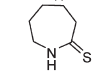
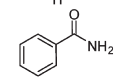
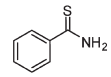
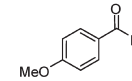
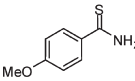
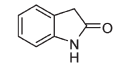
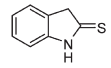
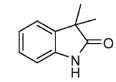
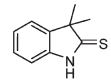
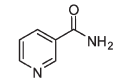
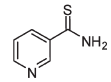
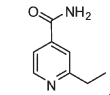
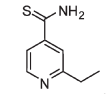
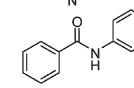
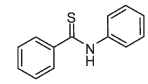
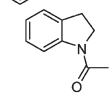
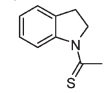
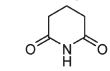
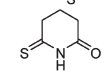
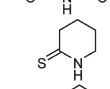
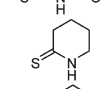
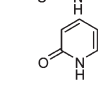
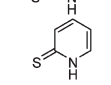
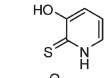
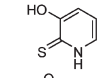
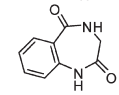
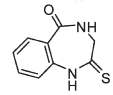
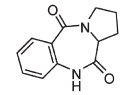
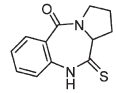
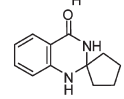
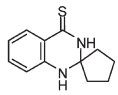
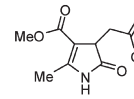
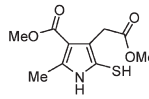
The crystal structure of the reagent **2a** has been determined by Grossman,[51] and now the structure of **3** has been confirmed by X-ray analysis, the details of which are given in the Experimental Section, and an ORTEP representation of the molecular structure is shown in Figure 3. The molecules are linked together via several van der Waal interactions. The strongest van der Waal contact (C−H···S) links the molecules together into and infinite chain along the *c*-axis. The packing coefficient (percent filled van der Waals space in the unit-cell) is 67.7%, indicating an efficient molecular framework in the solid state. The molecular packing is facilitated by the aromatic π stacking. The distance between the planes of two adjacent aromatic moieties is approximately 3.5 Å.

Very recently, a related structure, namely **17** (Figure 2), has been determined using X-ray crystallography.[52] This molecule was prepared by heating P_4S_{10} in pyridine together with S_8. The capacity of **17** to act as a thionating agent is so far unknown.

The structure of **11a** was confirmed by X-ray analysis, the details of which are given in the Experimental Section, and an ORTEP representation of the molecular structure is shown in Figure 4.

The outcome of a number of thionation experiments with the zwitterionic reagent **3** in hot acetonitrile are listed in Table 1. The ratio to reactant was always 1.1:4. In other words, it is assumed that the central sulfur atom is devoid of thionating power. In some cases, direct comparisons with **2a** have been made. For instance, ε-caprolactam and **3** gave the corresponding thioamide within 5 min, but **2a** thionates even faster. Actually, a suspension of **2a** in hot acetonitrile can be titrated by addition of ε-caprolactam. The advantage of **3** over **2a** is primarily that **3** is easier to prepare, odorless (when sufficiently pure) and that the

Table 1. Thionations of Amides with the Reagent 3 in Hot MeCN

entry	amide	thioamide	yield (%)	mp °C (lit. mp °C)
1			98	114-116 (114-115)[57]
2			98	115-116 (112-114)[58]
3			99	105.5-106.5 (103-104)[29,57]
4			85	117 (117-118)[20]
5			88	147-148 (147.5-148.5)[59]
6			Low yield See, Table 3, entry 13	144-145 (144-147)[53]
7			94	106-107 (107-108)[60]
8			90	195 (190-192)[61]
9			82	164-165 (164-164.5)[62]
10			96	99-100 (99-100)[63]
11			92[a]	110 [a, 64,65]
12			85	130-132 (135)[56]
13			90	92-93 (92-93)[16,57]
14			72	127-128 (128)[66,67]
15			65	141 (142-144)[68,69]
16			63	277-280 (277-283)[17]
17			87	268-270 (253-254)[70]
18			89	210-212 (decomp.)
19	 **34a**	 **34b**	81	185-187
20	**21a**	**21b**	79[b]	122

[a] Isolated product contained two rotamers (in agreement with previous reports[64,65]). [b] HRMS (EI+) *m*/*z* calcd for $C_{12}H_{11}NS$: 201.0612, found 201.0621.

dx.doi.org/10.1021/jo101865y |*J. Org. Chem.* 2011, 76, 1546–1553

thionated products are very pure. Formation of nitriles from primary amides never was a problem. This type of side reaction can sometimes be problematic when the reagent **2a** is used.[27,29] Thionation of ketones with **3** worked well provided that electron-donating groups are present as in **18a** and **18b** (Table 2, entries 3 and 4). The keto derivatives **20a** and **21a** could be converted to **20b** and **21b**, respectively, when the reagent **3** is used in hot pyridine or as a melt or even better, when heated together with dimethyl sulfone (Table 1, entry 20, and Table 3, entry 3).

Whereas thionation of 3,3-dimethyloxindole (entry 7, Table 1) gave an excellent yield, the parent compound, oxindole (entry 6, Table 1) gave unacceptably low yields (~10%). Here, formation of complexes of low solubility seems to be the cause of the problems. For synthesis of this molecule, indoline-2-thione, the method by Pedras (P_4S_{10} + $NaHCO_3$ in THF) is recommended.[53] Synthesis of 3,3-diindolylindoline-2-thione also failed but could be effected with dimethyl sulfone as solvent (see Table 3). Thionation of 3-hydroxy-2-pyridone worked well without complications to give the interesting class of 3-hydroxy-2-(1*H*)-pyridinethione, which for several types of metal complexes (e.g., Zn^{2+}) have shown some promise against diabetes mellitus.[54] Forceful conditions, namely treatment of 3-hydroxy-2-pyridone with P_4S_{10} at 200 °C had previously been used for synthesis of this class of compounds.[55]

Thionation of 3-hydroxy-2-quinolone similarly gave the known thione (Table 2, entry 6) which previously had been synthesized by a different technique.

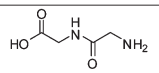
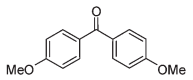
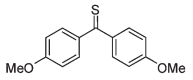
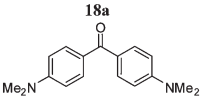
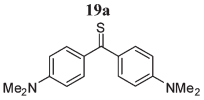
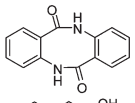
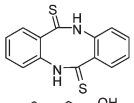
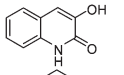
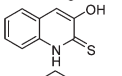
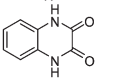
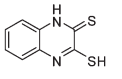
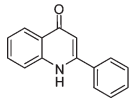
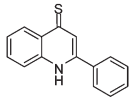
In cases where more than one carbonyl group is present in the starting materials, selectivity could be achieved. Thus, the monothionated molecules (Table 1, entries 12, 16, and 17) could be obtained in good yields. Thionation of piperidine-2,6-dione gave the monothionated product in hot acetonitrile, whereas with an excess of the reagent in hot pyridine the fully thionated product could be obtained. These two molecules had previously been synthesized and characterized a long time ago by Berg and Sandström.[56]

Thionation of Gly-Gly as well as piperazine-2,5-dione both gave good yields of the expected dithionated product (Table 2, entries 1 and 2). To further characterize the rather insoluble product, it was acetylated in hot acetic anhydride, which yielded the tetraacetylated product **35** (Figure 7), which readily gave nice NMR spectra.

Thionations at quite high temperatures (165−175 °C) could be affected with suitable reactants and the reagent **3** dissolved in dimethyl sulfone (mp 107−109 °C, bp 238 °C). The results are listed in Table 3. In one case (Table 3, entry 6) the product was partially converted to the highly insoluble disulfide **22**. Similar observations have been reported by Stoyanov[78,79] and Hino et al.[80] The latter workers found that a number of 3-substituted indole-2-thiones readily could be oxidized to the corresponding disulfides. Formation of oxidative products could be avoided by running the reactions under argon. Thionation of oxindole has also been studied under these high temperature conditions, at first, without air protection. The product obtained was high melting and had the composition $C_{16}H_{10}N_2S_2$, a clear indication that oxidative couplings had occurred. This product was tentatively assigned either structure **23** or structure **24** (Figure 5).

The alternative **24** could soon be ruled out because reductive cleavage of two S−S bonds with sodium borohydride in THF of the known molecule **25**[25,81] (an X-ray structure is available[25]) gave the dianion **26** (Figure 5), which when exposed to air slowly

Table 2. Thionations with the Reagent 3 in Hot Pyridine

entry	amide/ketone	thioamide/thione	yield (%)	mp °C (lit. mp °C)
1			78[a]	285 (285)[71]
2			90[b]	285 (285)[71]
3	 **18a**	 **19a**	82	120-121[72]
4	 **18b**	 **19b**	74	200-202 (200-202)[19]
5			96	297-298 (304-305)[73]
6			93	>260 (306-308)[74]
7			90	105-106 (105-106)[56]
8			83	298-300 (290-295 decomp.)[75,76]
9			77	192-194 (192-194)[77]

[a] Obtained from DMF−H_2O. [b] The spectral data were identical with the product from entry 1.

gave the pentacyclic molecule **23**, which proved to be identical with the product $C_{10}H_{10}N_2S_2$ discussed above. On the other hand, acidification of the dianion **26** immediately gave the corresponding acid which existed exclusively as the thione tautomer **27**. The diagnostic aliphatic hydrogen atoms resonated at 60.8 ppm in the ^{13}C NMR spectrum. Quenching of the dianion with dimethyl sulfate gave, as expected, 2,2′-bis-methylthiolo-3,3′-biindolyl, a known molecule.[81]

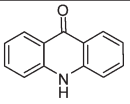
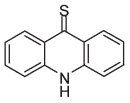
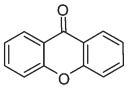
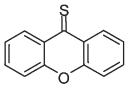
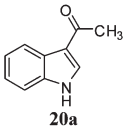
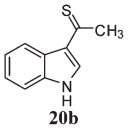
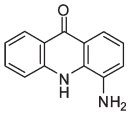
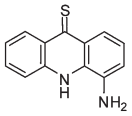
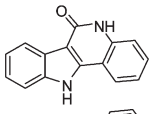
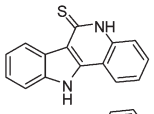
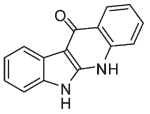
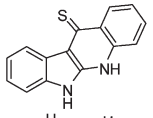
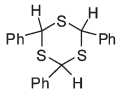
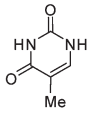
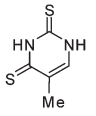
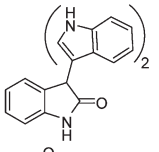
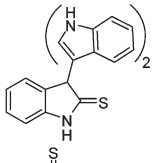
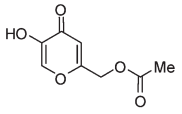
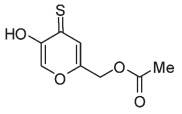
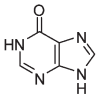
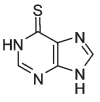
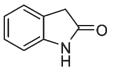
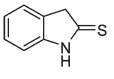
The alleged reductive transformation (**25** → **23**) had previously been described by Carpenter et al.,[81] but it seems likely that the product isolated at the time was the dithione **27** and not the claimed pentacycle **23**. The bisthione **27** has now been characterized for the first time. In contrast, its *N*,*N*-dimethyl derivative has, due to work by Hino et al., been known since 1969.[82] The structure of this derivative has also been confirmed by X-ray crystallography.[83] It should also be added that compound **23** is much more stable than its previously studied isomer **28**, which has a strong tendency to undergo dimerization.[84]

Benzaldehyde has been thionated many times in the past,[85−90] and the product has invariably been isolated as the trimer (**30**) of the unstable primary product **29** (Figure 6), and the trimer **30**, was indeed the product when benzaldehyde was reacted with the reagent **3** in dimethyl sulfone.

Ester carbonyl groups are generally not attacked by the reagent **3** as can be exemplified by thionation (Table 3, entry 10) of the monoacetate of kojic acid (**31**), which selectively gave the thione **32** (Table 1, entry 17). Thionation of the diester **33a**, obtained by addition of methyl β-aminocrotonate to maleic anhydride followed by esterification with methanol according to

dx.doi.org/10.1021/jo101865y |*J. Org. Chem.* 2011, 76, 1546–1553

Table 3. Thionations in Dimethyl Sulfone with 3 at 165−175 °C

entry	carbonyl compound	thiocarbonyl compound	yield (%)	mp °C (lit. mp °C)
1			90	274-276 (274-276)[93]
2			78	155 (157)[27,94]
3	 **20a**	 **20b**	53	144-145 (148-149)[95]
4			76	243-245 (244-248)[96,97]
5			95	335-337 (335-337)[98,99]
6			96	>260 (>260)[100]
7			62	228 (226)[90,101]
8			78	280-282 (283-285)[22] ^{1}H-NMR in agreement with data given in ref.
9			94	>260
10			56	114-115 (114-115)[102]
11			85	>260 (305-310 decomp.)[103,104] NMR in agreement with data given in ref. 94.
12			92	>284 (>285)[71]
13			92[a]	144-145 (144-145)[53]

[a] Experiment run under argon.

a literature procedure,[91] offered an other example, namely the pyrrole-2-thiol derivative **34b** (Figure 7).

The starting material existed completely (NMR evidence) as the tautomer **33a**, whereas the product existed completely as the thiol

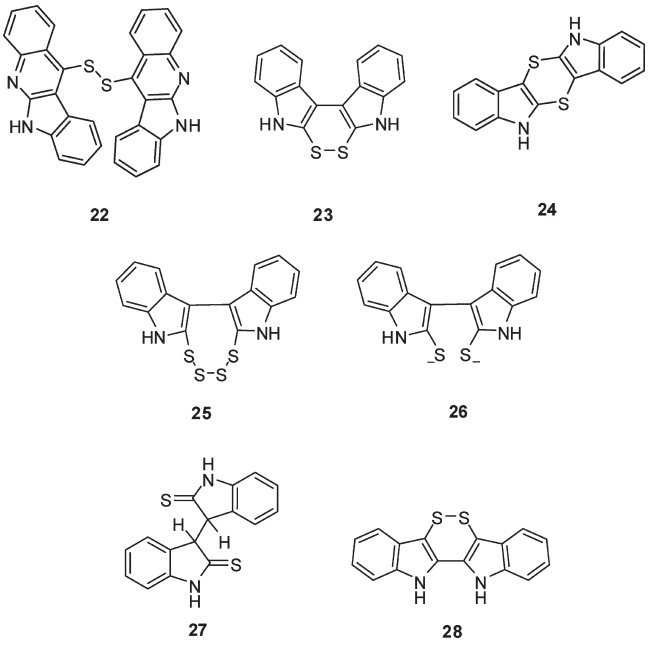


Figure 5. Graphical representation of molecular structures **22**−**28**.

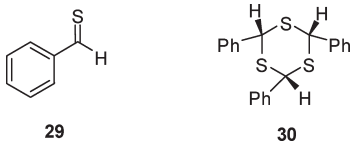


Figure 6. Structures of benzothialdehyde (**29**) and its corresponding trimer (**30**).

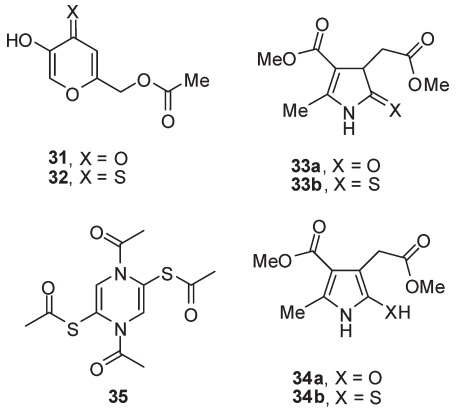


Figure 7. Structures of monoacetate of kojic acid (**31**), its thionated derivative (**32**), and structures **33**−**35**.

tautomer **34b**. But, more importantly, the two ester functions were intact. These results, are in nice agreement with general predictions about the tautomeric situation, given by Elguero.[92] Due to low solubility and high melting point, 2,5-piperazinedithione (Table 3, entry 12) was difficult to characterize; therefore, the readily soluble tetraacetate **35** was prepared.

CONCLUSIONS

The structure of the reagent obtained by reaction of P_4S_{10} with pyridine has been determined. This crystalline and storable

dx.doi.org/10.1021/jo101865y |J. Org. Chem. 2011, 76, 1546–1553

reagent is free from impurities inherent in the conventional reagent because these impurities (from P_4S_{10}) are removed via the pyridine mother liquor.

The improved purity will result in cleaner thionation products and more facile workup procedures. A particular advantage is the fact that the reagent can be transferred to other solvents such as acetonitrile and dimethyl sulfone.

EXPERIMENTAL SECTION

Reagent 3. Tetraphosphorus decasulfide (P_4S_{10}, 44.5 g, 0.1 mol) was added in portions to dry pyridine (560 mL) at 80 °C using stirring equipment. After a period of reflux (1 h), a clear yellow solution was obtained, which deposited light-yellow crystals when the solution was allowed to cool. After 2 h the crystals were collected, washed with dry acetonitrile and finally transferred to an exicator (containing a beaker with concd sulfuric acid) to remove any excess of pyridine: yield 62.3 g (84%); mp 167−169 °C; IR ν_{max} 3088, 3040, 1608, 1451, 1197, 1044, 723, 668 cm^{-1}.

Pyridinium Dihydrogen Monothiophosphate, 11a. The reagent **3** (3.80 g, 10 mmol) was heated at reflux temperature in acetonitrile (35 mL) containing water (1.0 mL). The clear solution (obtained within 3 min) was concentrated and the product allowed to crystallize, 3.15 g, (79%). The crystals were suitable for X-ray crystallography: mp 110−120 °C dec, with evolution of H_2S; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51 (m, 2H, 3-H), 7.95 (dd, 1H, 4-H), 8.63 (d, 2H, 2-H), 9.7 (br s, 3H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 124.7 (d), 138.5 (d), 147.8 (d).

Pyridinium *O,O*-Diethyldithiophosphonate 11b from 3. The reagent **3** (1.0 g) was heated at reflux in ethanol (5 mL) for 5 min, and the clear solution was evaporated to give an oil which soon solidified (100%): IR ν_{max} 2976, 2891, 1630, 1600, 1526, 1479, 1383, 1020, 920, 748, 681 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.08 (t, J = 7.1 Hz, 6H), 3.79 (m, 4H), 8.09 (m, 2H), 8.62 (m, 1H), 8.97 (m, 2H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 16.1 (q, $^3J_{C-P}$ = 8.8 Hz), 59.8 (t, $^2J_{C-P}$ = 7.1 Hz), 127.2 (d), 142.5 (d), 146.0 (d). The salt **11b** could also easily be prepared by neutralizing the known acid[38] **11c** with pyridine.

Thionations with 3 in Dimethyl Sulfone, General Procedure. The reactant (10 mmol) and the reagent **3** (3 mmol) plus dimethyl sulfone (5.0 g) were heated at 170−175 °C for 15 min. The solidified melt was added to boiling water. After 10−15 min, the separated product was collected and recrystallized if necessary.

Thionations with 3 in Acetonitrile, General Procedure. The reactant (40 mmol) and the reagent **3** (12 mmol) were heated at reflux temperature in acetonitrile (40 mL). A clear solution was usually quickly formed which within 15 min became turbid. After a period of reflux (30 min), the two-phase system was concentrated to ca. 20 mL, and water (30 mL) was added. A solid was quickly formed which was filtered, washed with water, and recrystallized if necessary to give pure product.

(*S*)-11-Thioxo-2,3,11,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo-[1,2-*a*][1,4]diazepin-5-(10*H*)-one (Table 1, Entry 17). To a MeCN solution (200 mL) of 2,3-dihydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*]-[1,4]diazepine-5,11(10*H*,11a*H*)-dione (4.3 g, 20 mmol) was added the reagent **3** (2.3 g, 6 mmol) and the mixture heated to 60 °C for 3 h during which time a yellow precipitate was formed. The reaction mixture was allowed to stand at room temperature overnight in order to precipitate fully. The product was vacuum-filtered and washed with a little cold MeCN to give the title compound (3.9 g, 85%) as a pale yellow solid: mp 268−270 °C (lit.[70] mp 253−254 °C); $[\alpha]^{23}_D$ +971 (*c* 0.16, MeOH) [lit.[70] $[\alpha]^{23}_D$ +873 (*c* 1.026, DMSO)]; IR ν_{max} 3170, 2979, 1616, 1602, 1477, 1374, 1271, 1141, 831, 813, 752 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.89−1.94 (m, 1H), 1.99−2.16 (m, 2H), 2.84−2.94 (m, 1H), 3.40−3.50 (m, 1H), 3.53−3.60 (m, 1H), 4.27 (d, J = 6.11 Hz, 1H), 7.22−7.27 (m, 1H), 7.30−7.37 (m, 1H), 7.55−7.60 (m, 1H), 7.80−7.85 (m, 1H), 12.46 (br s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 22.7(t), 29.0 (t), 46.8 (t), 59.8 (d), 121.8 (d), 125.7 (d), 127.8 (s), 130.2 (d), 132.2 (d),136.5 (s),164.2 (s), 201.9 (s).

Spiro[cyclopentane-1,2′(1′*H*)-quinazoline]-4′(3′*H*)-thione (Table 1, Entry 18). Reagent (0.96 g, 25 mmol) **3** was added to a suspension of spiro[cyclopentane-1,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (1.0 g, 5 mmol) in acetonitrile (50 mL), and the reaction mixture was heated at reflux for 7 h. After being cooled to room temperature, the dark-red solution was poured into water and allowed to stand in the refrigerator overnight. The precipitate was collected and washed with a small amount of cold MeCN to give the title compound (0.97 g, 89%) as orange flakes: mp 226 °C; IR ν_{max} 3389, 3254, 3128, 2966, 1612, 1531, 1468, 1235, 1148, 994, 748 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.65−1.69 (m, 4H), 1.76−1.80 (m, 2H), 1.88−1.95 (m, 2H), 6.65−6.71 (2H, m), 7.08 (s, 1H), 7.24 (t, J = 7.6 Hz, 1H), 8.04 (d, J = 7.9 Hz, 1H), 10.29 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ ppm 22.2 (t), 38.5 (t), 77.1 (s), 114.8 (d), 116.9 (d), 119.4 (s), 131.4 (d), 133.7 (d), 143.6 (s), 188.5 (s). Anal. Calcd for $C_{12}H_{14}N_2S$: C, 66.02; H, 6.46; N, 12.83. Found: C, 65.92; H, 6.11; N, 12.53.

2,5-Piperazinedithione from Glycine (Table 2, Entry 1). Glycine (1.50 g, 20 mmol), the reagent **3** (10.64 g, 28 mmol), and dimethyl sulfone (8.0 g) were heated at 165−170 °C for 1 h, whereupon the reaction mixture (after cooling) was treated with boiling water for 30 min. The brownish solid obtained was recrystallized from ethanol/DMF, 1.85 g (63%): mp 284 °C (lit.[71] mp 285 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.19 (s), 10.7 (s) [lit.[71] 4.22, 7.23 ppm (we consider that this reported signal for the −NH protons is in error)]; ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 54.4 (q), 191.9 (s) [lit.[71] 54.1, 193.7].

2,5-Piperazinedithione from 2,5-Piperazinedione (Table 2, Entry 2). 2,5-Piperazinedione (2.28 g, 20 mmol) and the reagent **3** (2.28 g, 8 mmol) were heated at reflux in acetonitrile (50 mL) for 2 h, when the mixture was concentrated and water was added. The solid formed was collected after a stirring period of 1 h, 2.63 g (90%). Melting point and NMR data are identical to data reported above for 2,5-piperazinedithione from glycine (Table 2, entry 1).

***S,S′*-1,4-Diacetyl-2,5-bis-acetylthiolo-1,4-dihydropyrazine, 35.** The above 2,5-piperazinedithione (1.46 g, 10 mmol) was heated at reflux temperature in acetic anhydride (20 mL) for 2 h, whereupon the reaction mixture was concentrated and treated with diisopropyl ether, 2.92 g (93%): mp 190−192 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.17 (s, 6H), 2.45 (s, 6H), 6.99 (s, 2H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 22.2 (q), 29.4 (q), 117.0 (s), 131.6 (d), 166.3 (s), 193.7 (s). Anal. Calcd for $C_{12}H_{14}N_2O_4S_2$: C, 45.75; H, 4.48; N, 8.88. Found: C, 45.90; H, 4.32; N, 8.71.

Reductive Cleavage of the Tetrasulfide, 25. The 3,3′-diindolyl-2,2′-tetrasulfide **25** (3.58 g, 10 mmol) was dissolved in THF (50 mL) and added to a mixture of $NaBH_4$ (1.50 g, 40 mmol) in THF (75 mL). Evolution of gases containing H_2S ensued, and the reaction mixture was stirred for 3 h at 40−45 °C under a blanket of argon. This air-sensitive solution containing the dianion **26** was not stored but directly transformed by operations described below.

2,2′-Bis(methylthio)-1*H*,1′*H*-3,3′-biindole. Dimethyl sulfate (1.51 g, 10 mmol) dissolved in MeOH (15 mL) was added dropwise to a solution obtained by reductive cleavage of the tetrasulfide **25** (5 mmol) at 25 °C. After a period (1 h) of stirring, the solution was evaporated and treated with water. The crude solid was crystallized from MeOH−water to yield a yellow solid (0.92 g, 57%): mp 184−186 °C (lit.[81] mp 187−188 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.07 (s, 6H), 7.04−7.08 (m, 2H), 7.28−7.33 (m, 4H), 7.49−7.51 (m, 2H), 12.16 (s, 2H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 18.0 (q), 110.8 (s), 110.9 (d), 119.0 (d), 119.2 (d), 121.5 (d), 128.0 (s), 129.1 (s), 137.0 (s).

Synthesis of the Cyclodisulfide, 23. A solution obtained by reductive cleavage of the tetrasulfide **25** was, after addition of water

dx.doi.org/10.1021/jo101865y |*J. Org. Chem.* 2011, 76, 1546–1553

(50 mL), stirred for 24 h in contact with air. The yellow solid formed was collected and crystallized from acetonitrile−DMF 4:1 yielding 2.20 g (77%) of a solid still containing DMF, which was removed by drying under reduced pressure: mp >227−228 °C (lit.[81] mp 206−208 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.04−7.08 (m, 1H), 7.28−7.31 (m, 2H), 7.33−7.51 (m, 1H), 12.16 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 136.3 (s), 127.0 (s), 124.9 (s), 124.6 (d), 120.3 (d), 120.2 (d), 119.3 (s), 112.2 (d).

Cyclodisulfide 23 by Thionation of Oxindole at 160 °C (Table 3, Entry 13). Oxindole (1.33 g, 10 mmol) and the reagent **3** (1.52 g, 4 mmol) were warmed with dimethyl sulfone (4. 0 g) and then heated at 160 °C for 5 min. The melt was allowed to cool and then heated with water. The solid formed was crystallized from acetonitrile−DMF 4:1 yielding 1.37 g (92%): mp >227−228 °C. This material was identical with that obtained via reductive cleavage of the tetrasulfide **25**.

3,3′-Bithio-oxindole, 27. The solution obtained from reductive cleavage of the tetrasulfide **25** was acidified with AcOH, which resulted in quick formation of the title compound as a yellow precipitate, 2.52 g (85%). The precipitate was recrystallized from acetonitrile, mp 180 °C dec. This molecule is sensitive toward aerial oxidation: ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.66 (s, 2H), 6.85−6.91 (m, 4H), 6.96−6.98 (m, 2H), 7.07−7.13 (m, 2H), 13.06 (s, 2H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 60.8 (d), 110.4 (d), 123.0 (d), 123.4 (d), 128.6 (d), 130.2 (s), 144.2 (s), 204.3 (s). Anal. Calcd for $C_{16}H_{12}N_2S_2$: C, 64.60; H, 4.08; N, 9.43. Found: C, 64.26; H, 3.99; N, 9.31.

Methyl 5-Mercapto-4-(2-methoxy-2-oxoethyl)-2-methyl-1*H*-pyrrole-3-carboxylate, 34b. The diester **33a** (2.13 g, 10 mmol) and the reagent **3** (1.14 g, 4 mmol) were heated at reflux temperature in acetonitrile (50 mL) for 1 h. After concentration to 25 mL, water was added and the solid formed collected and crystallized from 2-propanol, 1.85 g (81%): mp 185−187 °C; IR ν_{max} 3273, 2954, 1742, 1724, 1707, 1681, 1562, 1440, 1341, 1269, 1200, 1173, 1117, 1080, 1003, 782 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.43 (s, 3H), 3.17 (s, 2H), 3.38 (s, 1H), 3.49 (s, 3H), 3.64 (s, 3H), 11.90 (s 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 13.4 (q), 30.6 (d), 50.4 (q), 51.4 (q), 111.2 (s), 117.1 (s), 126.9 (s), 139.9 (s), 164.4 (s), 171.1 (s)Anal. Calcd for $C_{10}H_{13}NO_4S$: C, 49.37; H, 5.38; N 5.75. Found: C, 49.25; H, 5.46; N, 5.61.

3-(1*H*-Indol-3-yl)-3,3′-biindoline-2-thione (Table 3, Entry 9). 3-(1*H*-Indol-3-yl)-3,3′-biindolin-2-one[105] (728 mg, 2 mmol), the reagent **3** (228 mg, 0.6 mmol), and dimethyl sulfone (3.05 g) were heated (165−170 °C) for 20 min. The melt was allowed to cool and then heated in water for 10 min. The solid formed was collected, 713 mg (94%): mp >260 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.09−7.15 (m, 2H), 7.18−7.20 (m, 5H), 7.24−7.30 (m, 7H), 13.00 (s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 72.7 (s), 111.2 (d), 124.4 (d), 126.5 (d), 127.5 (d), 128.6 (d), 128.7 (d), 129.0 (d), 129.1 (d), 129.1 (d), 139.2 (s), 143.0 (s), 143.5 (s), 145.3 (s, 2C), 208.4 (s). Anal. Calcd for $C_{24}H_{17}N_3S$: C, 75.96; H, 4.51; N, 11.07. Found: C, 76.10; H, 4.46; N, 11.00.

■ ASSOCIATED CONTENT

Supporting Information. The crystal structural data of **3** and **11a** have been deposited at Cambridge Data Centre and allocated the deposition numbers CCDC 789665 and CCDC 789666. CIFs for compounds **3** and **11a** are included. Experimental details for 6*H*-indolo[2,3-*b*]quinolin-11-one and compounds **13a** and **33a** (Table 1, entries 2, 3, and 8). Compound characterization data for 6*H*-indolo[2,3-*b*]quinolin-11-one and compounds **13a** and **33a** (Table 1, entries 2, 3, 8, and 11; Table 3, entries 3, 7, and 10). Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. Copies of ^{1}H NMR are provided for most compounds in the tables. This material is available free of charge via the Internet at http://pubs.acs.org.

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