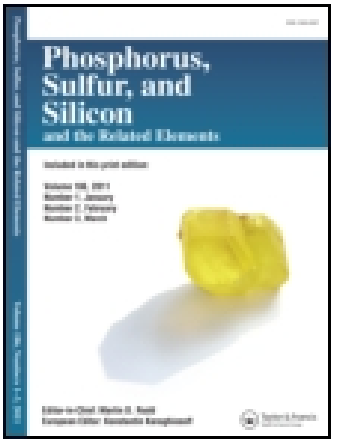

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New Reactions of the Thiocarbonyl Function. The Synthesis of Hindered Peptides

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New Reactions of the Thiocarbonyl Function. The Synthesis of Hindered Peptides.

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ABSTRACT: The well-known radical chemistry of the thiocarbonyl function has been expanded to include the concerted reaction between an *O*-acyl derivative of *N*-hydroxypyridine-2(1*H*)-thione (a Barton PTOC ester) and a sulfenamide. The atom-economical process spawned a carboxamide and an unsymmetrical disulfide of synthetic and biological value. The reaction was successfully applied to the synthesis of sterically encumbered, urethane-protected dipeptides. The oxidation-reduction technology pertaining to the disulfide-phosphine combination facilitated the generation of transient Barton PTOC esters. In conjunction with the appropriate benzenesulfenamide, the Barton PTOC ester of benzoyl-L-leucine was shown to preserve optical integrity according to the sensitive Young test, albeit at low temperature. However, the thermodynamic forces at play are powerful and, as a result, the yields were not compromised. In all but the sterically demanding instances, the parent free amine almost matched the reaction time, yield, and enantiomeric excess of the corresponding benzenesulfenamide in its reaction with a Barton PTOC ester.

KEY WORDS: Barton PTOC esters, sulfenamides, concerted mechanism, steric hindrance, oxidation-reduction condensation, optical integrity.

INTRODUCTION

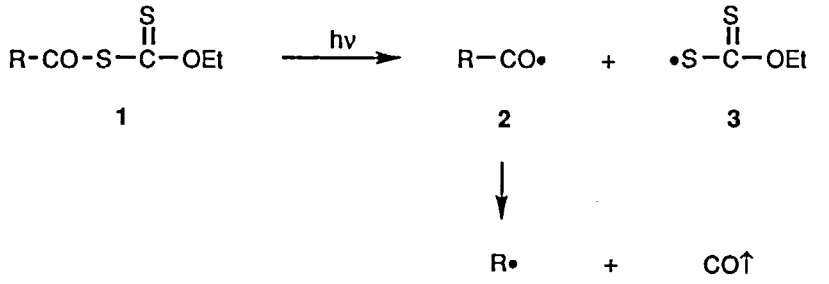
The thiocarbonyl function has a more interesting reactivity than that of the conventional carbonyl group. Examples from the past include the photochemistry of acyl xanthates to afford acyl radicals, and the similar reaction of homoallylic thionobenzoates to afford olefins and thiobenzoic acid quantitatively. More recently, the radical chemistry of the thiocarbonyl function has served in an efficient and useful deoxygenation reaction well known to carbohydrate chemists. A later development was the coordination of the radicophilic properties of the thiocarbonyl function that culminated in the formation of acyloxy radicals. By decarboxylation *in situ*, a clean source of alkyl radicals became available.

Now, in a new chapter on thiocarbonyl chemistry, the application of the acyl derivatives of thiohydroxamic acids (Barton PTOC esters) in the synthesis of peptides, is presented. The driving force of the reaction is such that both *N*-methylated and α,α-dialkylated peptides can be synthesized without difficulty.

DISCUSSION

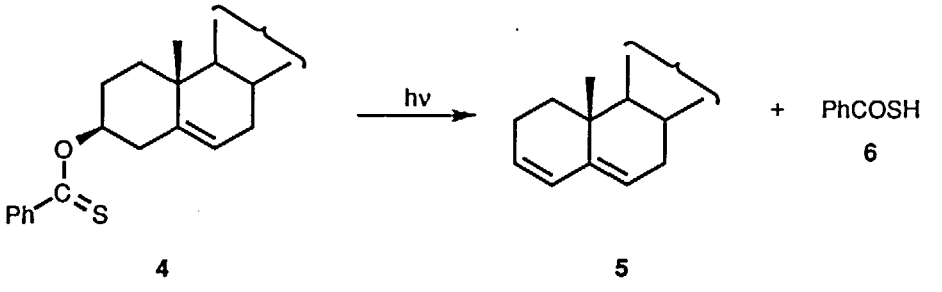
A Compendium of Our Contributions

A first meeting with the thiocarbonyl group took place in 1962.[1] It was predicted that the photolysis of acyl xanthates **1**, then a little known class of compounds, might furnish acyl radicals **2** and xanthate radicals **3**. This prediction was verified through experiment. Depending on the substitution pattern and the temperature, the acyl radicals decomposed to alkyl radicals and carbon monoxide (**Scheme 1**). Quite recently, Zard[2] has brilliantly developed the application of this initial reaction into a whole series of new and synthetically useful reactions.



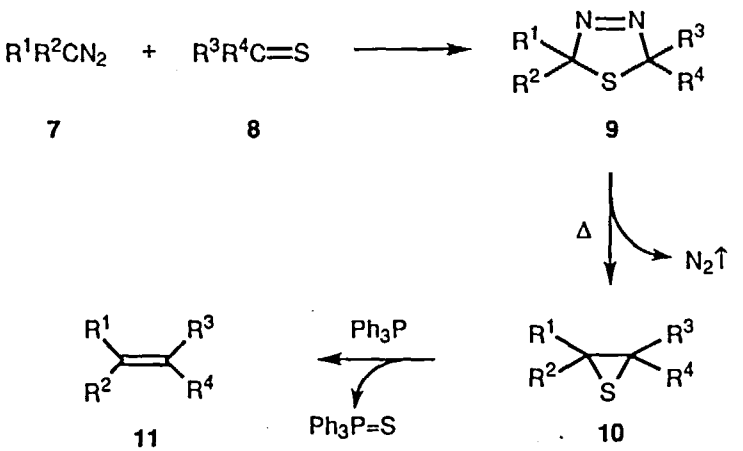
SCHEME 1

A second thiocarbonyl reaction of general interest was discovered accidentally in 1973.[3] A solution of freshly prepared cholesterol thionobenzoate **4** in ether was left on a bench for several days. The yellow color disappeared. Cholesta-3,5-diene **5** and thiobenzoic acid **6** were formed quantitatively (**Scheme 2**). This type of reaction was later generalized and shown to occur under very mild conditions (-78 to 0°C) using a tungsten lamp. The mechanism of the reaction was also determined and shown to involve the lowest $n\pi^*$ state.[4] In spite of the mild conditions and excellent yield, this reaction has not yet been used in synthesis.



SCHEME 2

The next thiocarbonyl-based reaction that was predicted turned out to have spectacular value for the synthesis of very hindered olefins.[5] As shown in **Scheme 3**, it was conceived that a diazo-compound **7** could react with a thione **8** to afford an adduct **9**. For unhindered compounds this reaction was already known.[6] However, it had never been appreciated that this was an excellent route to very hindered olefins. With **9** in hand, heating in the presence of triphenylphosphine afforded the sulfide **10** that was at once desulfurized to give the desired hindered olefin **11**. By this two-fold extrusion, the olefin **11** (R^1, R^2 = phenyl; R^3, R^4 = *t*-butyl) was readily prepared in good yield. Even di-*t*-butylfenchylidene **11** (R^1, R^2 = fenchylidene; R^3, R^4 = *t*-butyl) could be made. The synthesis was improved by using selenoketones (selones) which were prepared in perfectly stable form for the first time.[5] However, we failed to make the most hindered olefin of all -- tetra-*t*-butylethylene **11** (R^1, R^2, R^3, R^4 = *t*-butyl). All efforts since have also failed.[7] This synthetic objective still remains the Holy Grail of hindered molecules.

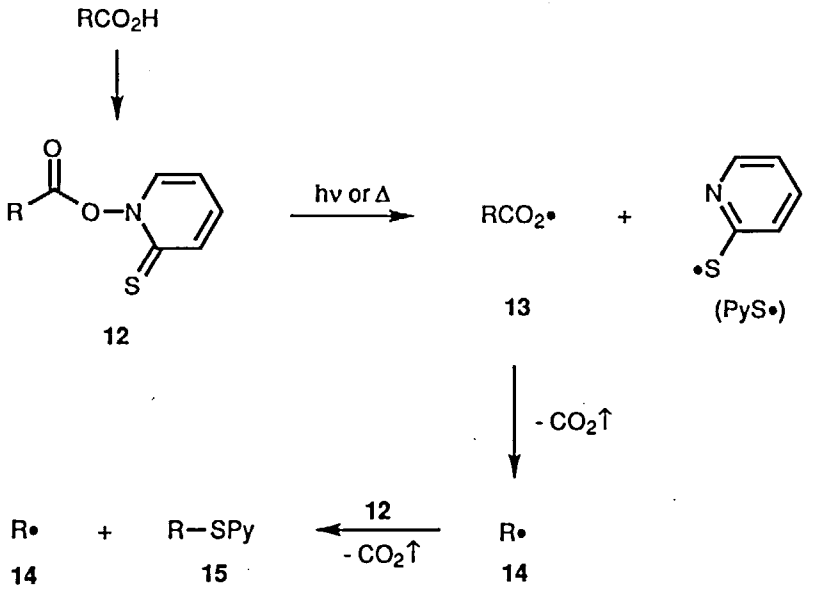


SCHEME 3

It was the Schering-Plough Corporation who, because of their great success with the aminoglycoside antibiotic *Gentamycin*, first demonstrated that a new method was needed for the deoxygenation of sugar-based secondary alcohols. To avoid the problems of neighboring group participation, the solution could not be a conventional ionic reaction. Thus the thiocarbonyl route for deoxygenation (the Barton-McCombie reaction) was invented for this particular purpose. It was a spectacular success.[8]

The Barton-McCombie reaction can be used for the generation and cyclization of carbon radicals as well as for deoxygenation. However, a more elegant solution to the problem of the synthesis of "disciplined" carbon radicals came from the invention of the Barton decarboxylation reaction.[9] The essence of this reaction is summarized in **Scheme 4**. An aliphatic or alicyclic carboxylic acid RCO_2H is condensed with *N*-hydroxy

pyridine-2(1*H*)-thione to furnish an acyl derivative **12**. This class of compounds provides a convenient source of carbon radicals either by irradiation with visible light or by heating at 80-100°C in an inert solvent. The carboxyl radical initially formed, **13**, rapidly loses carbon dioxide to furnish the carbon radical **14**. This can react efficiently with a variety of traps. The termination of the reaction is the capture of the radical, or a derived radical, by the "disciplinary" thiocarbonyl group. In the absence of a trap, the standard rearrangement reaction takes place to furnish **15** with reformation of the radical **14**. The quantum yields in this type of reaction have been determined.[10] Numerous other thiohydroxamic acids have been studied. Their acyl derivatives all show the same propensity for radical generation. Even more sensitive derivatives have been prepared.[11]



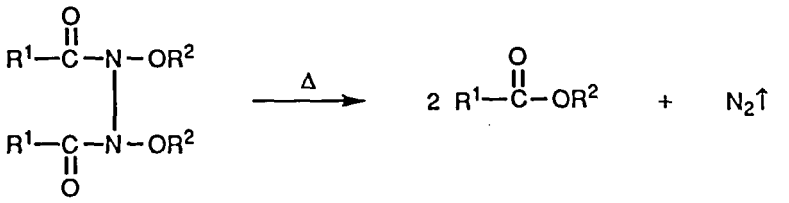
SCHEME 4

Against this background of successful radical generation, the potentiality of the acyl derivatives **12** for ionic chemistry has been largely ignored. Based on two papers that will appear in *Tetrahedron*[12] later this year, it is the purpose of this article to show that there remains much useful ionic chemistry still to be explored. This work, again, is based on the special properties of the thiocarbonyl function.

Barton PTOC Esters and Sulfenamides

Our search for easily-removable carbohydrate- and peptide-based carboxylic acid protecting groups fortuitously led us to the *N,N'*-diacyl-*N,N'*-dialkoxyhydrazines **16**.[13] These *O*-alkyl hydroxamate dimers were first reported by Crawford and Raap in 1963[14]

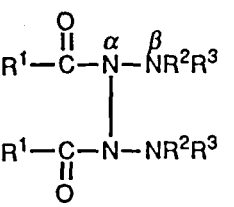
and were subsequently shown to be facile progenitors of carboxylate esters **17** and dinitrogen (**Scheme 5**).[15] We, and others,[16] have shown that the thermally induced collapse of the hydrazine derivative **16** proceeds in an intramolecular, concerted fashion that involves two three-centered processes around each of the nitrogen atoms. The reactions of amides involving HEteroatom Rearrangements On Nitrogen have thus been termed the "HERON" rearrangements.[17]



16 **17**

SCHEME 5

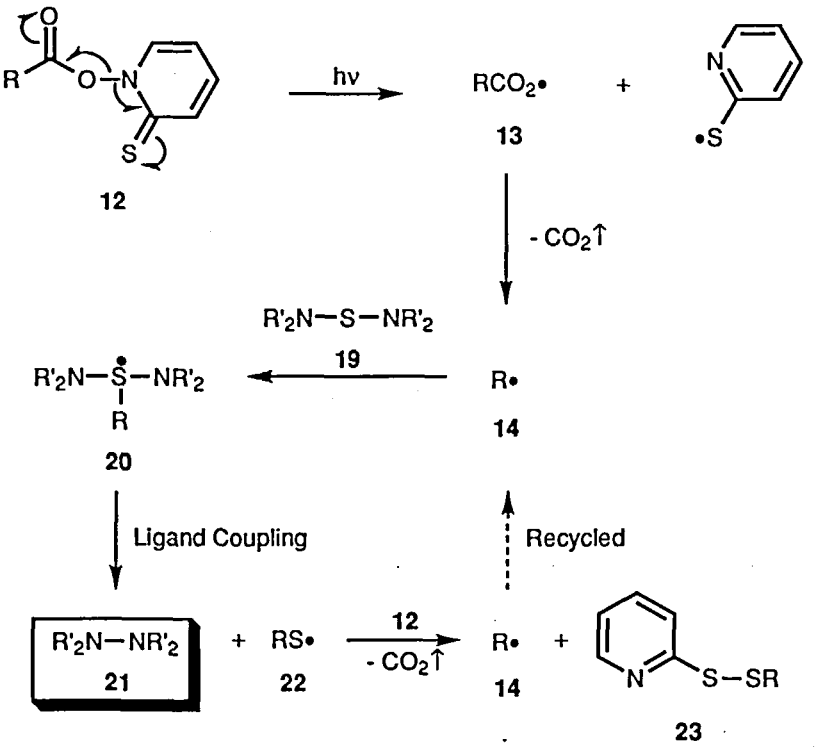
The relative ease with which the dimer **16** (R^1 = 1-adamantanyl; R^2 = *t*-butyl) collapsed to form the highly hindered ester **17** (R^1 = 1-adamantanyl; R^2 = *t*-butyl),[13] piqued our interest in compounds of structure **18**. It is conceivable that these *β,β*-dialkyl hydrazide dimers can similarly undergo a HERON rearrangement to give the corresponding carboxamides. In the case of steric congestion, this transformation would prove to be a worthwhile accomplishment since the construction of these ostensibly simple carboxylic acid derivatives remains perplexing.



18

The synthesis of **18**, however, proved troublesome. In related studies, we found that *β,β*-dialkyl hydrazides did not dimerize under oxidative conditions but, instead, furnished tetrazine derivatives.[18] Perusal of the literature deterred us from conventional ionic chemistry since the HERON rearrangement of *α*-chlorinated *β,β*-dialkyl hydrazides was shown to be more propitious than nucleophilic displacement.[17] We therefore took recourse to radical chemistry and contemplated the reaction between a Barton PTOC ester **12** and an *N,N'*-thiodiamine **19** as delineated in **Scheme 6**.[12] The acronym "PTOC" was coined by Newcomb and denotes the Pyridine-2-Thione-*N*-OxyCarbonyl moiety.[19]

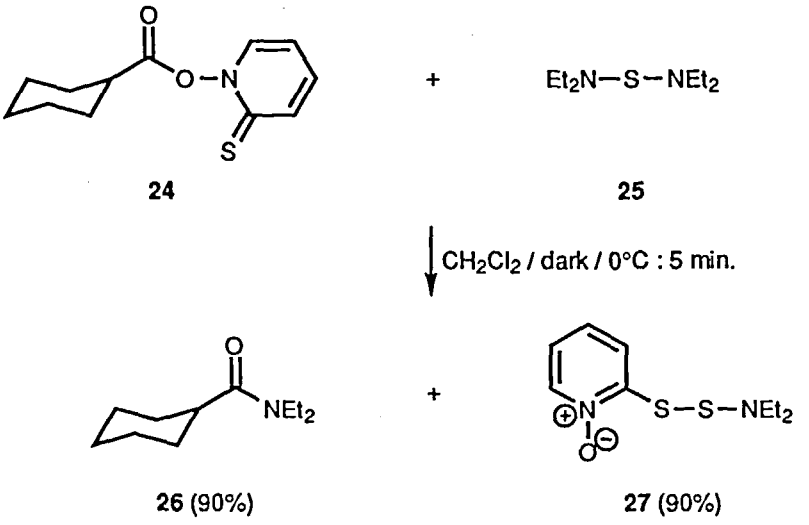
As we have already mentioned (*vide supra*), the aliphatic and alicyclic Barton PTOC esters are carbon-centered radical generators *par excellence* and, in the presence of **19**, could lead to the formation of the complex radical **20**. Subsequent intramolecular collapse could liberate the desired hydrazine **21** and the sulfur-centered radical **22**.[20] The latter could then rebound onto the precursor **12**. This is tantamount to saying that the innately tempestuous free radical **22** is "disciplined" by the thiocarbonyl function of **12**. Decarboxylation would eventually regenerate the carbon-centered radical **14** and the 2-alkyldithiopyridine **23**. *Ergo*, a radical chain process was envisaged with **22** functioning as the chain carrier.



SCHEME 6

This conjecture was put to the test when the Barton PTOC ester **24** and the *N,N'*-thiodiamine **25** were mixed in equimolar amounts at 0°C in the dark and under an argon atmosphere (**Scheme 7**). Surprisingly, the starting materials were instantaneously consumed *before* the onset of photolysis. The carboxamide **26** and the unsymmetrical disulfide **27** were isolated, both in 90% yield. At 0°C and under continuous irradiation with a 100 W tungsten lamp, none of the products that would arise from the original hypothesis (*cf.* **Scheme 6**), or from the decarboxylative rearrangement that is the hallmark of Barton PTOC ester radical chemistry (*cf.* **Scheme 4**), were detected. The

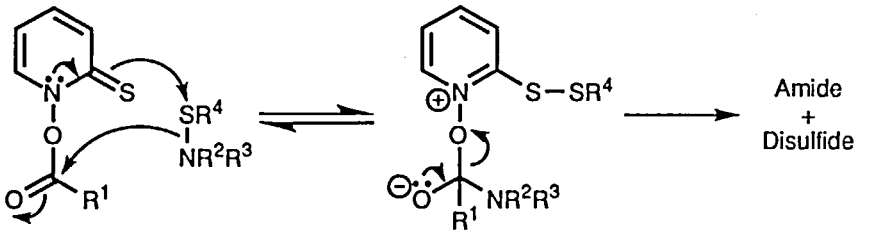
reaction displayed a GC-determined half-life of 20 minutes at -30°C and at an 0.1 M concentration of the reactants.



SCHEME 7

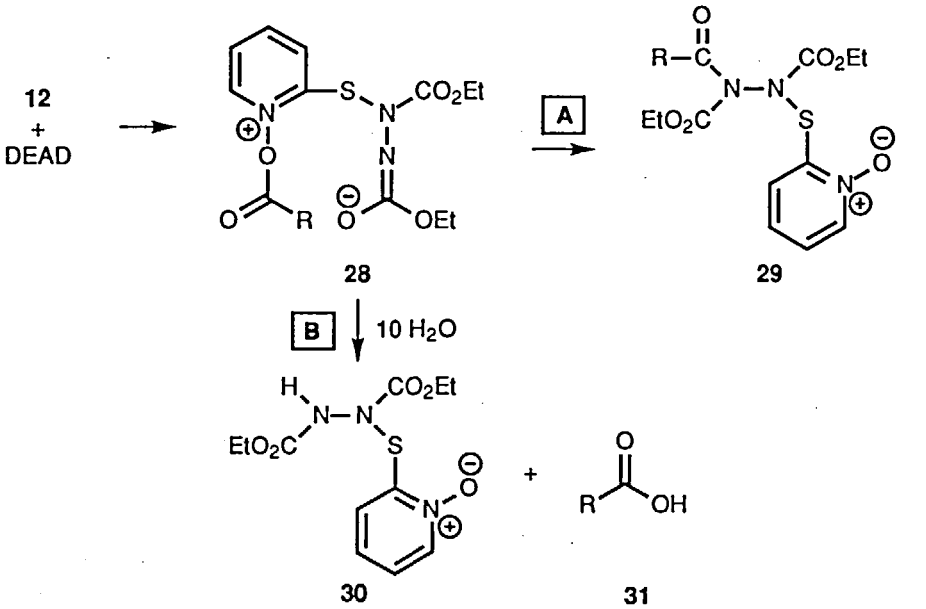
It is known that various carboxylic acid derivatives react with sulfenamides (of which the *N,N'*-thiodiamines are a subdivision) to give carboxamides, *inter alia*.[21] These reactions do, however, require a trivalent phosphine in either catalytic or stoichiometric amounts to induce the reaction through labilization of the S-N bond. The fact that the reaction depicted in **Scheme 7** did not require such external catalysis and directly produced a carboxamide (thereby circumventing the need for the HERON rearrangement of a hydrazide dimer such as **18**), merited closer scrutiny. It was found that the reaction required an apolar, aprotic solvent such as dichloromethane (preferentially) or tetrahydrofuran. The reaction tolerated moderate quantities of water as a nucleophile (the reactants hydrolyze only sluggishly without a catalyst) and as a weak proton source (no intermediates were intercepted). Polar additives (Grieco's 5.0 M $LiClO_4$-Et_2O,[22] for example) and S-N bond-labilizing, low-valent transition metals such as Cr(0)[23] did not accelerate the sterically demanding instances (*vide infra*). The presence of a radical trap such as the 2,2,6,6-tetramethylpiperidinyl-1-oxy free radical (TEMPO) did not alter the distribution of products. The evidence at hand therefore suggested a mechanism that departs from the classical view by which the sulfenamides interact with electrophiles.[24] In our opinion, Barton PTOC esters and sulfenamides react in a concerted fashion that involves a seven-membered transition state. This mechanism is drawn in **Scheme 8.** The reaction is thermodynamically driven by the formation of the relatively stable carboxamide function, by the aromatization of the 2-thiopyridone moiety and, to a lesser

extent, by sulfur's natural tendency to catenate (that is, by formation of the disulfide bond).



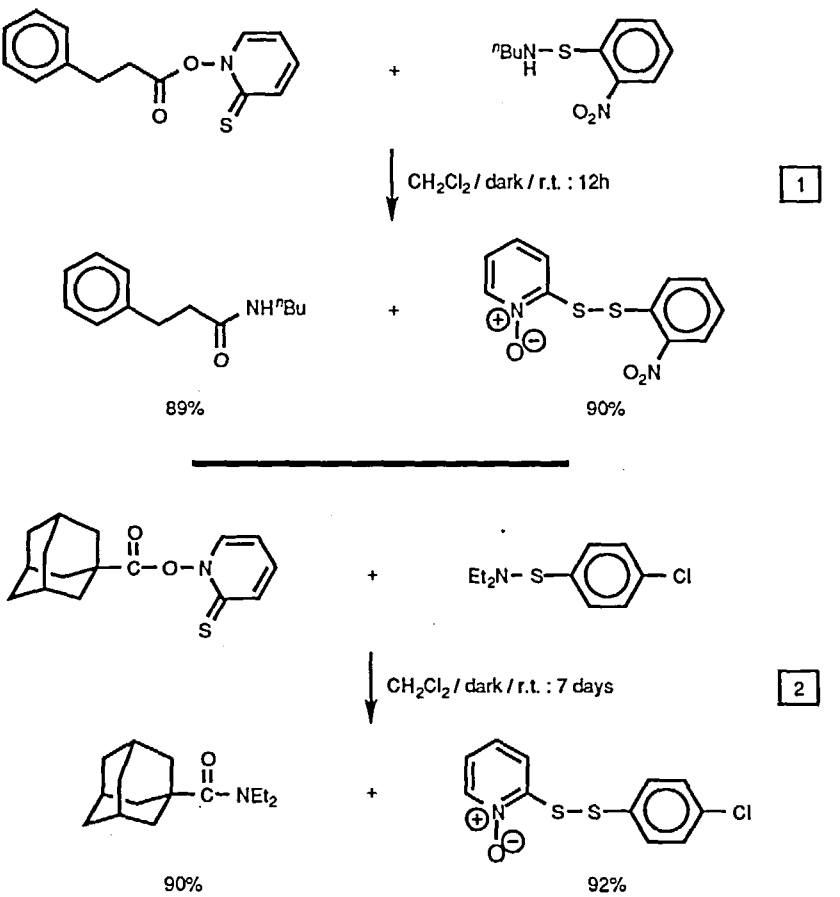
SCHEME 8

The mechanism drawn in **Scheme 8** is not without precedent. It bears close resemblance to the mechanics we invoked to account for the adducts that arose when Barton PTOC esters and diethyl azodicarboxylate (DEAD) were allowed to react.[25] In a reinvestigation of this reaction, we demonstrated the ionic nature of the adduct-forming process (**Scheme 9**). In the presence of a ten-fold excess of water, compounds of structure **29** were not formed since the adduct-spawning manifold **A** was shunted to the hydrolysis manifold **B**. The latter furnished the hydrazine derivative **30** and a carboxylic acid **31**. The isolation of **30** provided tangible evidence that the reaction undoubtedly crosses the intermediate **28**.

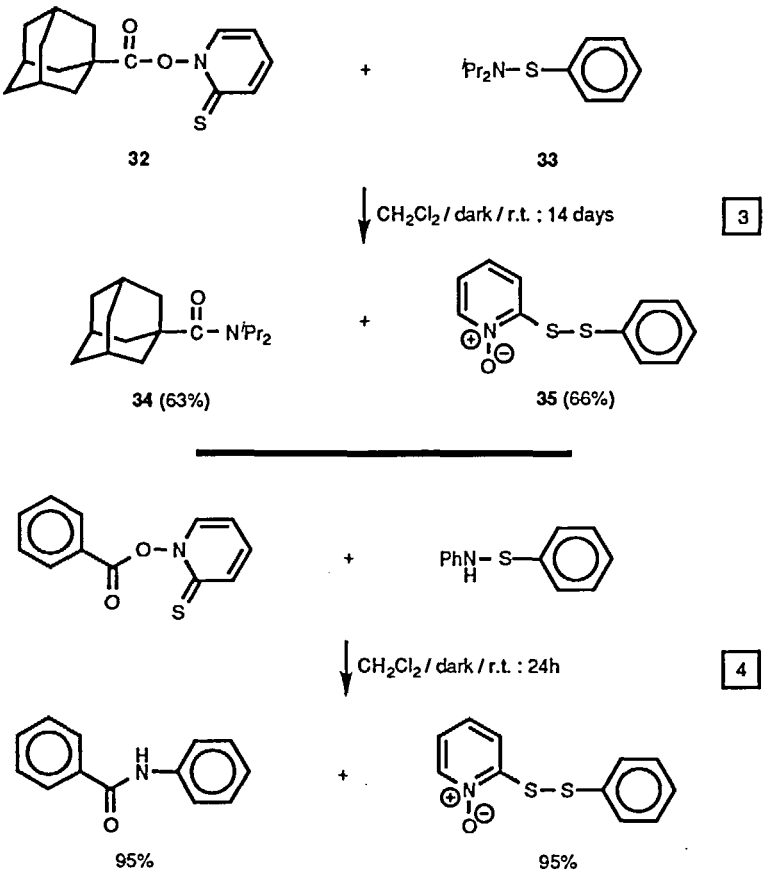


SCHEME 9

The reaction with an *N,N'*-thiodiamine has already been discussed (*cf.* **Scheme 7**). In cases where steric burden decelerated the reaction, the thermal instability of these compounds led to complex reaction mixtures and, accordingly, to diminished yields. The stability and, hence, the reactivity of the arenesulfenamides could be tailored for optimal reaction. This versatility resides in the choice of the aromatic substituent on the sulfenamide *S*-atom (**Scheme 10**). We found that the stable, chromatographable 2-nitrobenzenesulfenamides presented the best compromise between reactivity and stability for the transfer of primary amines such as *n*-butylamine (Reaction (1)). The 4-chloro benzenesulfenamides were several orders of magnitude more reactive and facilitated the transfer of secondary amines such as diethylamine (Reaction (2)). The unsubstituted benzenesulfenamides were ultimately found to be the reagents of choice for the transfer of sterically crowded secondary amines such as diisopropylamine (Reaction (3)). The transfer of a relatively weak amine nucleophile -- aniline, for example -- did not present a problem either (Reaction (4)).



SCHEME 10

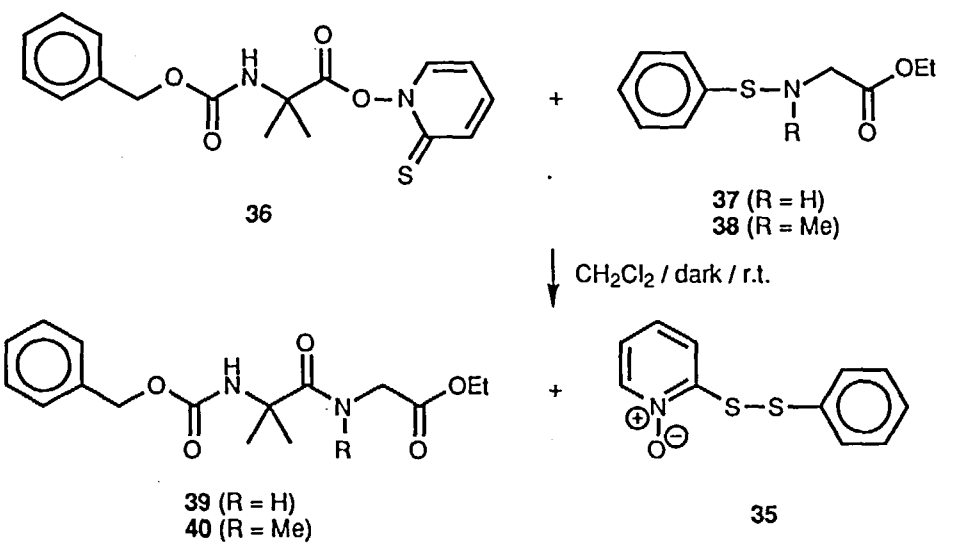


SCHEME 10 (continued)

The union of a Barton PTOC ester and a sulfenamide[26] spawned a carboxamide and, concomitantly, an unsymmetrical disulfide. In this regard, the reaction represents another example of an atom-economical process[27]: The entire array of atoms in the reactants is expressed in the products. We have successfully applied the unsymmetrical disulfides as sulfenylating agents.[28] Biologically, their ability as antimicrobial agents has been established. The disulfide **35**, for example, is particularly effective in curbing the yeast *Pityrosporum ovale* that is commonly found in the human scalp and frequently associated with the dandruff syndrome.[29] The carboxamide function is the repeating unit in the biologically important polypeptide macromolecules. In recent years, the construction of sterically congested carboxamides has been the subject of intense investigation. In particular, the incorporation of either *N*-methylated or α,α-dialkylated amino acid residues into peptides represents a difficult, albeit worthwhile, exercise.[30] Peptides that contain these residues often exhibit significant biological activity. This is the case with, for example, *Cyclosporin A*. This cyclic undecapeptide, which contains no

less than seven *N*-methylated α-amino acid residues, is the active ingredient of the immunosuppressive drug "Sandimmune" that is used to prevent graft rejection in bone marrow and organ transplants.[31]

We demonstrated that the reaction between a Barton PTOC ester and a sulfenamide affords a viable addition to the modern array of solution-phase peptide coupling methods. As is illustrated in **Scheme 11**, benzyloxycarbonyl-protected α-aminoisobutyric acid (Z-Aib) was activated at the carboxy terminus by derivatization to the corresponding Barton PTOC ester **36**. The α-amino acid esters ethyl glycinate (Gly-OEt) and ethyl sarcosinate (Sar-OEt) were activated at their *N*-termini by derivatization to the respective benzenesulfenamides, **37** and **38**. Subsequent stoichiometric coupling afforded the dipeptide **39** (Z-Aib-Gly-OEt) and the very hindered **40** (Z-Aib-Sar-OEt) in excellent yields (**Table I**). The unsymmetrical disulfide **35** was easily separated from the dipeptides by flash column chromatography over silica gel and was obtained in nearly quantitative yield. Our preparation of **39** must be compared with that of Frérot *et al.*[32] who constructed this urethane-protected dipeptide using various members of the powerful BOP-family, *viz.* BOP (92% yield), PyBOP® (87%), BroP (89%), and PyBroP (87%). Along with a comparable reaction time (one hour) and a superior yield (95%), our protocol had the added advantage that carcinogenic by-products (HMPA in the case of BOP and BroP) were not produced. Moreover, our reaction was conducted under virtually neutral conditions. This derives from the fact that the arenesulfenamides have pK_b-values on the order of 10-11[33] and are, therefore, much less basic than, for example, the commonly employed diisopropylethylamine (DIEA) with a pK_b-value of 3.90.[34]

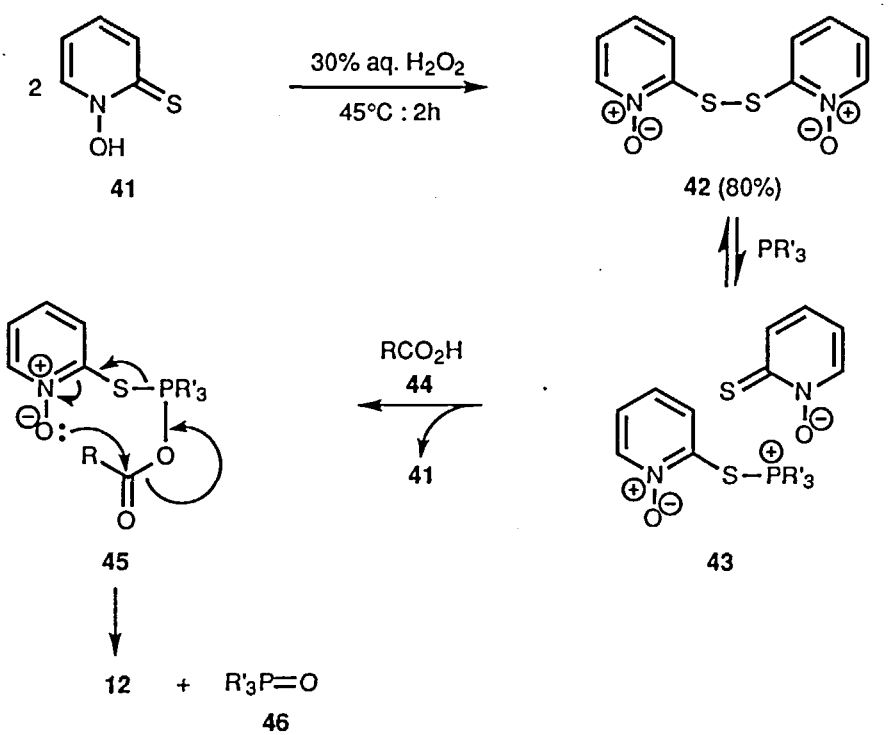


SCHEME 11

TABLE I
Reaction of Z-Aib Barton PTOC Ester **36** with α-Amino Acid Ester Benzenesulfenamides **37** and **38**.

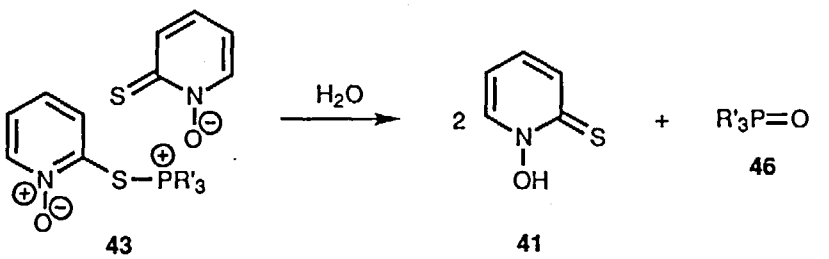
Entry	Sulfenamide	Dipeptide	Time (h)	% Isolated Yield	
				Dipeptide	**35**
1	**37**	**39**	1	95	97
2	**38**	**40**	12	92	99

More often than not, Barton PTOC esters can be isolated as perfectly stable, lime-green solids. Their propensity to spawn carbon-centered radicals is largely confined to the solution state. When it is required, however, these activated esters can be conveniently generated through the application of oxidation-reduction condensation -- a technique pioneered by Mukaiyama.[35] Our system comprises 2,2'-dithiodipyridine-1,1'-dioxide **42** (which is readily accessible from commercially available *N*-hydroxypyridine-2(1*H*)-thione **41**[36]) and a trivalent phosphine.[37]



SCHEME 12

The mechanics involved are delineated in **Scheme 12**. The reaction is governed by the remarkable affinity of trivalent phosphorus for free and bound sulfur.[38] Hence, **42** initially oxidizes the phosphine to the phosphonium salt **43**. The carboxylic acid **44** then reduces the latter to the acyloxyphosphorane **45**, thereby expanding the valence shell of phosphorus to ten electrons. Finally, **45** collapses -- presumably in an intramolecular fashion -- to the desired Barton PTOC ester **12** and the quinquevalent phosphine oxide **46**. Formation of the latter imparts a powerful thermodynamic driving force to this reaction: One estimate of the P=O bond energy is 130 kcal/mol.[39] The oxidation-reduction system has the additional advantage of being self-drying since the disulfide-phosphine combination rapidly and irreversibly reacts with water through the phosphonium salt **43**. Under neutral conditions, traces of moisture are thus expelled from the system as the thiohydroxamic acid **41** and the phosphine oxide **46** (**Scheme 13**).[40]

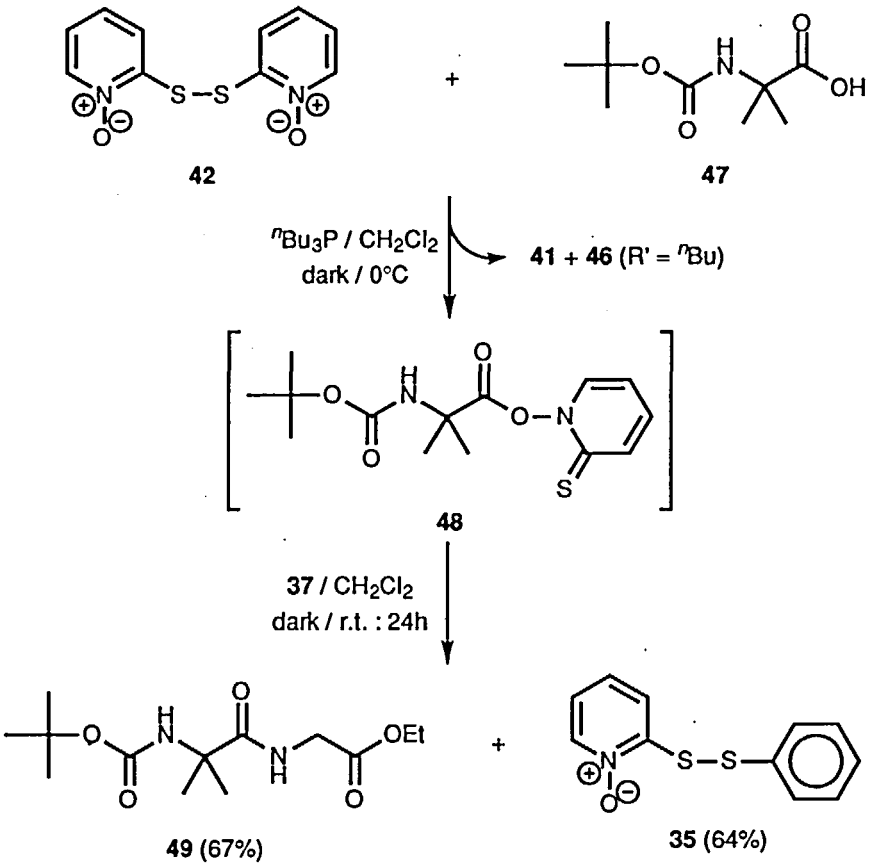


43 **41** **46**

SCHEME 13

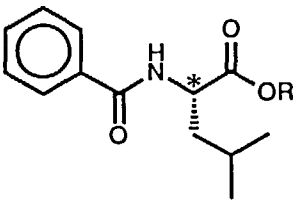
The generation and use of a transient Barton PTOC ester are illustrated in **Scheme 14**. The disulfide **42** and *t*-butyloxycarbonyl-protected α-aminoisobutyric acid **47** (Boc-Aib) rapidly condensed at 0°C under the influence of an equimolar amount of tri-*n*-butylphosphine to give the Barton PTOC ester **48**. Subsequent stoichiometric reaction with the benzenesulfenamide **37** (*cf.* **Scheme 11**) afforded the dipeptide **49** (Boc-Aib-Gly-OEt) and the unsymmetrical disulfide **35** in yields of 67 and 64%, respectively. Although the reaction system may appear complex, a mild acid-base work-up (to remove the expelled thiohydroxamic acid **41**) and flash column chromatography over silica gel (to separate **35**, **46** and **49**) sufficed to obtain analytically pure products. In this case, tri-*n*-butylphosphine was used as the source of trivalent phosphorus. Triphenylphosphine, although less nucleophilic, is cheaper and works equally well.[41]

The oxidation-reduction protocol proved invaluable when the Barton PTOC ester-benzenesulfenamide couple was probed for the preservation of optical integrity. The classical Young test[42] formed the basis of our experiment and required the Barton PTOC

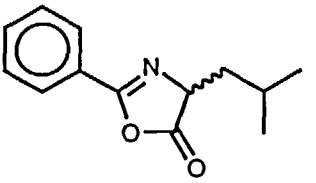


SCHEME 14

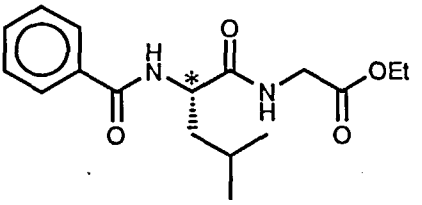
ester **51** of the racemization-prone benzoyl-L-leucine **50**. It is known that this racemization is due to the oxazolone **52**.[43] In accord with the observations of Williams and Young[42], the DCC-method -- our mainstay for obtaining isolated Barton PTOC esters -- overactivated the carboxy terminus of **50** and afforded unacceptably large quantities of the racemized Young-dipeptide **53**. We were able to surmount this difficulty by application of the oxidation-reduction protocol. The results are summarized in **Scheme 15** and **Table II**. Formation of the transient Barton PTOC ester **51** (process **A**) at a moderately low temperature did not lead to a significant enhancement in enantiomeric excess (entry 1). However, by progressively lowering the temperature (entries 2 and 3), racemization was virtually eliminated at *all* stages (that is, in both processes **A** and **B**) of the reaction sequence. On the basis of the supersensitive[44] Young test, we therefore concluded that the Barton PTOC ester-benzenesulfenamide couple preserves optical integrity under careful kinetic control. The very low temperature (-95°C) at which the phosphine was introduced in entry 3 was easily attained with a methanol-liquid nitrogen



50 (R = H)
51 (R = 2-Thiopyridone)

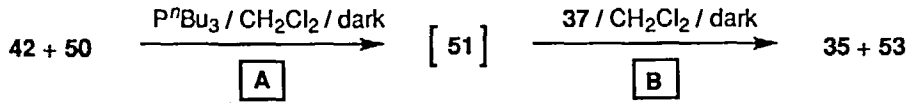


52



53

bath. This low temperature did not detract from the synthetic utility of the process: The thermodynamic forces at play are such that the yields of **35** and **53** (90% in each case) were not compromised.



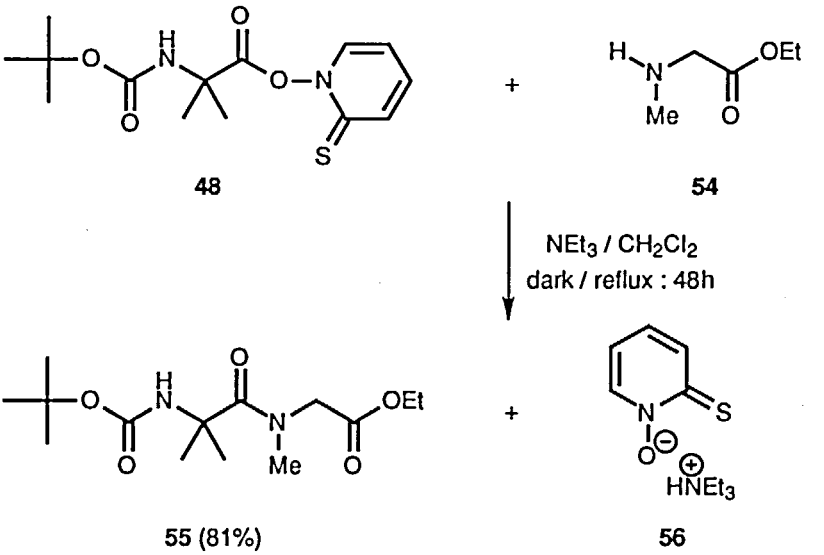
SCHEME 15

TABLE II
Effect of Reaction Conditions on the Racemization Observed in the Classical Young Test with Benzenesulfenamide **37**.

Entry	Reaction Conditions		$[\alpha]_D^{22}$	%ee[42]
	A	B	· (*c* 3.1, EtOH)	
1	0°C, then r.t. for 30 min.	0°C, then r.t. for 30 min.	-10.3°	30
2	-78°C for 90 min.	-78 → -20°C for 6h.	-29.5°	88
3	-95 → -78°C for 90 min.	-78 → -20°C for 12h.	-32.5°	96

Barton PTOC Esters and Free Amines

Commensurate with our studies on the sulfenamides, Barton PTOC esters were also reacted with the parent free amines.[45] The reaction is known for the analogous carboxylate esters of *N*-hydroxy-2(1*H*)-pyridone[46] but, apparently, has fallen into desuetude. A representative example is shown in **Scheme 16.** As is illustrated, the synthesis of the severely hindered dipeptide **55** (Boc-Aib-Sar-OEt) was achieved in 81% yield starting from the isolated Boc-Aib Barton PTOC ester **48** (*cf.* **Scheme 14**) and ethyl sarcosinate **54.**



SCHEME 16

The reaction with the free amines probably journeys across the well-known tetrahedral intermediate[47] and, therefore, does not involve the thiocarbonyl function. In cases where steric demand was negligible, the free amines mimicked the reaction time, yield, and enantiomeric excesses obtained with the corresponding benzenesulfenamides. In the sterically hindered instances, however, the latter proved to be the preferred reagents. For example, the benzenesulfenamide **33** reacted with the 1-adamantanyl Barton PTOC ester **32**, albeit slowly, to give the severely hindered carboxamide **34** in satisfactory yield (*cf.* Reaction (3) of **Scheme 10**). With the parent free diisopropylamine, on the other hand, no reaction could be induced under a variety of forcing conditions. These included, amongst others, using a large excess (ten molar equivalents) of the amine, elevated reaction temperatures (refluxing dichloromethane or tetrahydrofuran), and catalysis with any one of 4-dimethylaminopyridine, methyl iodide, and silver nitrate. In this regard, the thiocarbonyl function appears to be of paramount

importance: The coordination of the PTOC thiocarbonyl moiety to the sulfenamide *S*-atom inductively activates the sulfenamide *N*-atom and brings this "electronically enriched" atom in proximity to the electrophilic PTOC carbonyl group (*cf.* **Scheme 8**). These effects are absent in the tetrahedral mechanism that governs the reaction with the free amines.

In conclusion, we have shown that the *O*-acyl derivatives of *N*-hydroxypyridine-2(1*H*)-thione behaved as activated esters toward free primary and secondary amines and their sulfenamide counterparts. The reaction of a Barton PTOC ester and a free amine progressed by way of the tetrahedral mechanism and produced a carboxamide and an unavailing ammonium salt (**56**, for example). The union of a Barton PTOC ester and a sulfenamide, on the other hand, spawned a carboxamide and an unsymmetrical disulfide of some value. The latter reaction represents an atom-economical process. Except for an additional synthetic step, the benzenesulfenamides were the reagents of choice. To wit, the benzenesulfenamides were more reactive in the sterically hindered instances, preserved optical integrity to a slightly greater extent[12] in the Young test, and facilitated reaction under milder conditions because no free amine was present in the reaction system.

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