Pergamon

Tetrahedron, Vol. 52, No. 28, pp. 9347-9366, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00487-5

N-Hydroxypyridine-2(1*H*)-thione Derivatives of Carboxylic Acids as Activated Esters. Part I. The Synthesis of Carboxamides.

Derek H. R. Barton* and J. Albert Ferreira

Department of Chemistry, Texas A&M University, College Station, TX 77843-3255, USA.

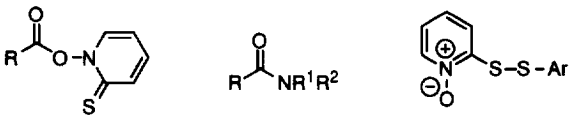
Abstract : The reaction between an acyl derivative of *N*-hydroxypyridine-2(1*H*)-thione (a Barton PTOC ester) and either an amine (primary or secondary), or the corresponding sulfenamide, led to the formation of a carboxamide in a clean transformation requiring minimal work-up and purification. The reaction with a sulfenamide is particularly useful since the only by-product, an unsymmetrical disulfide, is of both synthetic and biological value. In sterically demanding cases, Barton PTOC esters were more reactive towards benzenesulfenamides than to the corresponding free amines.

INTRODUCTION

We introduced the acyl derivatives of *N*-hydroxypyridine-2(1*H*)-thione as convenient and mild sources of disciplined, carbon-centered radicals more than a decade ago[1]. The so-called Barton PTOC esters[2] have since found pervasive synthetic use and the original concept has been extended to PTOC carbamates and *N*-alkoxypyridine-2(1*H*)-thiones to generate a plethora of nitrogen- and oxygen-centered radicals[3]. The "ionic" use of the *O*-acyl thiohydroxamates as activated carboxylic esters has, however, remained unexplored despite a report some thirty years ago that the analogous carboxylate esters of *N*-hydroxy-2(1*H*)-pyridone readily undergo nucleophilic displacement to produce carboxamides and dipeptides, amongst others, in good yield[4]. The carboxamide moiety is ubiquitous in nature and, as such, has piqued the interest of Organic Chemists since the inception of their science. The carboxamide group is, for example, the repeating unit in the biologically important polypeptide macromolecules and, accordingly, its construction and properties are of fundamental importance in this arena. Our interest in the ionic chemistry of Barton PTOC esters was spurred on by the fact that the synthesis of sterically congested carboxamides remains a conundrum[5] despite the plenitude of methods available for constructing less hindered analogs[6]. A solution to this challenging problem is of great current interest. For example, it is known that incorporation of *N*-methylated[7] (*e.g. Cyclosporin A*[8]) or α,α-dialkylated[9] (*e.g. Alamethicin F30*[10]) amino acid residues into peptides are difficult, but worthwhile, accomplishments since peptides containing these residues are of significant biological interest. However, many of the efficient coupling procedures in the oligopeptide arena fail when attempting to construct complex nucleoside antibiotics that contain peptide-like linkages[11].

The purpose of this article is to report our results on the use of Barton PTOC esters as general precursors to carboxamides. Relevance to the synthesis of peptides containing sterically congested amino acid residues will be illustrated in the following article.

RESULTS AND DISCUSSION

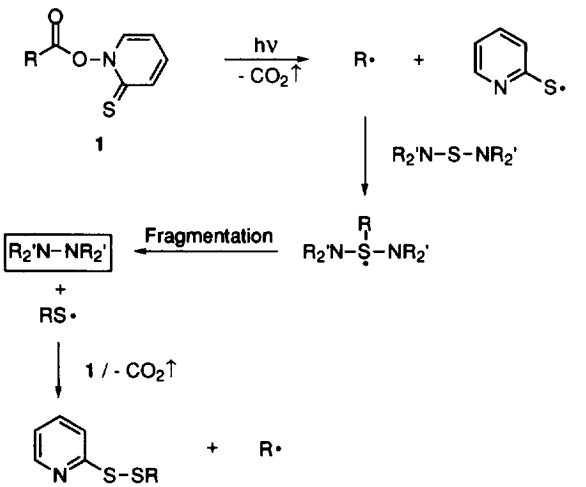


1 3 4

$R_2N-S-NR_2$ R^1R^2N-SAr

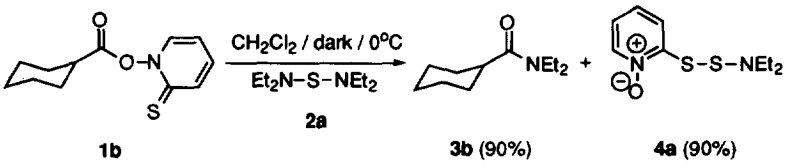
2 8

Barton PTOC Esters and Sulfenamides. As part of our ongoing research on the formation and use of the N-N linkage[12], we became interested in the reaction between a Barton PTOC ester **1** and a thiobisamine **2**. Our idea to explore radical chemistry to construct the N-N bond was based on recent reports that arenesulfenamides serve as convenient sources of aminyl radicals[13]. As depicted in **Scheme 1**, the carbon radical R• could, *in principle*, generate the complex radical shown which, by fragmentation, might produce the desired Et_2N-NEt_2.



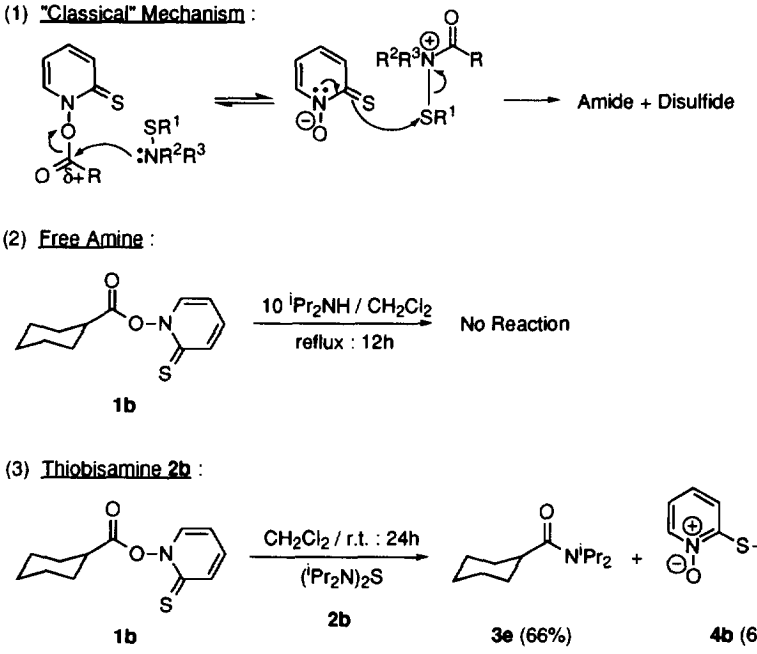
SCHEME 1

Contrary to this possibility, Barton PTOC ester **1b** and thiobisamine **2a** reacted instantaneously in stoichiometric amounts at 0°C to give carboxamide **3b** and the unsymmetrical disulfide **4a** in a high-yielding transformation *before* the onset of photolysis (**Scheme 2**). At -30°C and 0.1 M concentration of the reactants, the reaction displayed a half-life of 20 minutes.



SCHEME 2

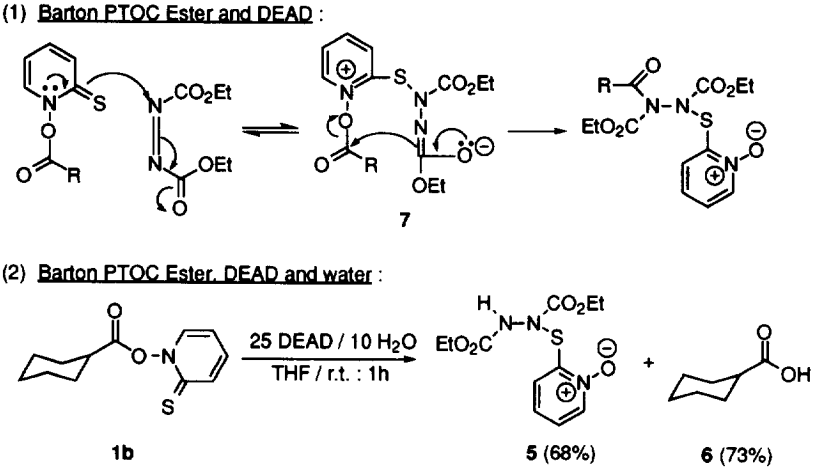
Sulfenamides are known to react with copper carboxylates[14], carboxylic acid anhydrides[15], acid halides[15] and *S*-esters of thiocarboxylic acids[16] to produce carboxamides in good yield. These reactions require the presence of a trivalent phosphorus compound (triphenylphosphine preferentially) in either stoichiometric or catalytic amounts to induce the reaction *via* labilization of the S-N bond. The ease of reaction between the Barton PTOC ester **1b** and the thiobisamine **2a** in the *absence* of a tertiary phosphine and the high isolated yield of products were thus surprising and prompted us to further investigate the reaction.



SCHEME 3

Mechanistically, three possible pathways for the reaction between a Barton PTOC ester and a sulfenamide (of which the thiobisamines are a subclass) can be envisaged. The first involves the "classical" mechanism by which the S-N bond interacts with electrophiles[17], in this case the PTOC carbonyl moiety. This counterattack-

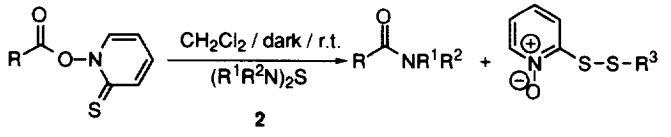
type mechanism is delineated in Equation (1) of **Scheme 3**. We argue against this on the basis that the sterically congested *free* diisopropylamine did not react with the Barton PTOC ester **1b** (Equation (2)) under a variety of forcing conditions (excess amine, reflux, external catalysis *via* methyl iodide and silver nitrate, *inter alia*) whereas the sulfenamide analogue **2b** gave a reasonable yield of the carboxamide **3e** and the unsymmetrical disulfide **4b** under mild conditions (Equation (3)).



SCHEME 4

Secondly, the mechanism invoked to account for the adducts that arise when Barton PTOC esters and diethyl azodicarboxylate (DEAD) react[18], was considered (Equation (1) of **Scheme 4**). When Barton PTOC ester **1b** was reacted with a 25-fold excess of DEAD in the presence of 10 equivalents of distilled water, the hydrazine derivative **5** and cyclohexanecarboxylic acid **6** were isolated in good yield (Equation (2)). The stable hydrazine derivative **5** provided tangible evidence that the reaction doubtlessly proceeds *via* intermediate **7**

(Equation (1)) which can be protonated (Equation (2)). Repetition of the reaction between the Barton PTOC ester **1b** and the thiobisamine **2a** in the presence of 1, 10 and 100 equivalents of distilled water did not, in any way, alter the rate of the reaction or the distribution of products. The ionic process drawn in Equation (3), therefore, does not fully account for the experimental observations. We propose that Barton PTOC esters and sulfenamides react in a concerted process (Equation (4)) that is resistant to the effects of an external nucleophile or a proton source. A radical mechanism can, of course, be dismissed as the reaction spontaneously proceeds in the dark[19] and, more importantly, the N-O bond of the Barton PTOC ester is not cleaved but recovered unscathed in the *N*-oxide moiety of the unsymmetrical disulfide. The reaction is propelled by formation of the thermodynamically stable carboxamide moiety and, to a lesser extent, by the formation of the disulfide bond. The latter provides yet another example of sulfur's innate propensity to catenate[20]. The reaction was subsequently applied to the three Barton PTOC esters **1a**, **1b** and **1c** as representative examples of simple primary, secondary and tertiary carboxylic acids. The results are summarized in **Scheme 5** and **Table 1**.



1a R = 2-phenethyl
1b R = cyclohexyl
1c R = 1-adamantanyl

2a $R^1 = R^2 = Et$
2b $R^1 = R^2 = {}^iPr$

4a $R^3 = NEt_2$
4b $R^3 = N^iPr_2$

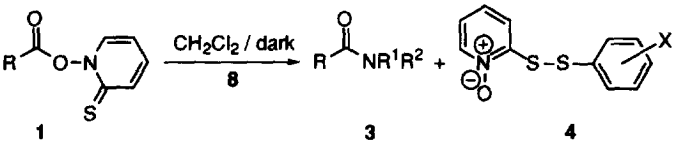
3a R = 2-phenethyl, $R^1 = R^2 = Et$
3b R = cyclohexyl, $R^1 = R^2 = Et$
3c R = 1-adamantanyl, $R^1 = R^2 = Et$
3d R = 2-phenethyl, $R^1 = R^2 = {}^iPr$
3e R = cyclohexyl, $R^1 = R^2 = {}^iPr$
3f R = 1-adamantanyl, $R^1 = R^2 = {}^iPr$

SCHEME 5

TABLE 1. Reaction of Barton PTOC Esters **1a-1c** with Thiobisamines **2a** and **2b**

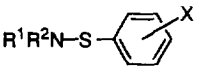
Entry	1	2	3	4	Time (h)	% Isolated Yield	
						3	4
1	**1a**		**3a**		0.5	90	86
2	**1b**	**2a**	**3b**	**4a**	0.5	90	90
3	**1c**		**3c**		12	53	62
4	**1a**		**3d**		24	59	61
5	**1b**	**2b**	**3e**	**4b**	24	66	63
6	**1c**		**3f**		30	7	8

The yields in **Table 1** are by no means impressive. This is ascribed to the fact that the thiobisamines **2** are thermally unstable[21] leading, with time, to complex reaction mixtures that required extensive work-up and purification with an inevitable decrease in yield (entries 3-6). We therefore took recourse to the more stable, substituted arenesulfenamides **8** that would not significantly decompose in cases where steric congestion demanded longer reaction times. The results of this refinement are synopsized in **Scheme 6** and **Table 2.**



3g R = 2-phenethyl, R^1 = *n*-Bu, R^2 = H
3h R = cyclohexyl, R^1 = *n*-Bu, R^2 = H
3i R = 1-adamantanyl, R^1 = *n*-Bu, R^2 = H

4c X = 2-NO_2
4d X = 4-Cl



8

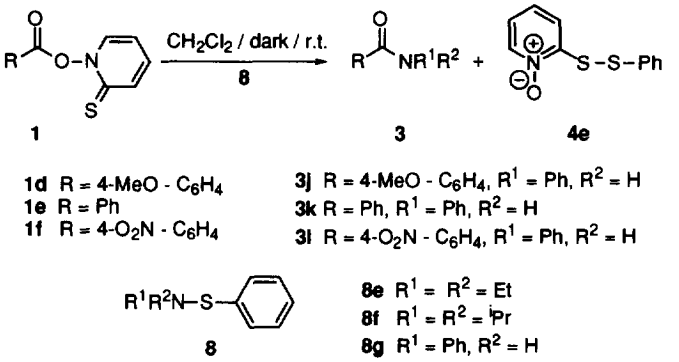
8a R^1 = *n*-Bu, R^2 = H, X = 2-NO_2
8b R^1 = R^2 = Et, X = 2-NO_2
8c R^1 = R^2 = Et, X = 4-Cl
8d R^1 = R^2 = ^{i}Pr, X = 4-Cl

SCHEME 6

TABLE 2. Reaction of Barton PTOC Esters **1a-1c** with Monosubstituted Arenesulfenamides **8a-8d**

Entry	1	8	3	4	Conditions	% Isolated Yield	
						3	4
1	**1a**		**3g**		r.t. : 12h	89	90
2	**1b**	**8a**	**3h**	**4c**	r.t. : 24h	88	91
3	**1c**		**3i**		r.t. : 48h	86	88
4	**1a**		**3a**		r.t. : 60h	78	81
5	**1b**	**8b**	**3b**	**4c**	reflux : 24h	78	78
6	**1c**		**3c**		reflux : 24h	---	---
7	**1a**		**3a**		r.t. : 12h	88	89
8	**1b**	**8c**	**3b**	**4d**	r.t. : 24h	91	86
9	**1c**		**3c**		r.t. : 7 days	90	92
10	**1a**		**3d**		r.t. : 5 days	89	87
11	**1b**	**8d**	**3e**	**4d**	r.t. : 7 days	66	63
12	**1c**		**3f**		reflux : 7 days	10	11

Introduction of an electronegative group on the sulfenyl side of the S-N linkage imparted sufficient stability to sulfenamides **8a** - **8d**, *ergo* permitting longer reaction times and cleaner mixtures in sterically arduous instances (entries 10-12). The 2-nitro group served this purpose well for *n*-butylamine (entries 1-3). In the case of diethylamine (entries 4-6), however, the increased S-N bond order[22] proved detrimental to reaction efficiency (entry 6). When the 2-nitro group was replaced with the 4-chloro atom, the resulting sulfenamides **8c** and **8d** readily afforded the desired carboxamides **3a-3e** in respectable yields (entries 7-11). As shown in **Scheme 7** and **Table 3**, omission of an electron-withdrawing substituent on the sulfenyl aromatic ring ultimately provided reactive benzenesulfenamides **8e-8f** of sufficient stability that allowed for clean and relatively high-yielding transformations in simple (entries 1-3) and sterically more demanding cases (entries 4-6). The reaction was also used to transfer a relatively weak amine nucleophile, aniline, to carbonyl groups of increasing electrophilicity (entries 7-9).



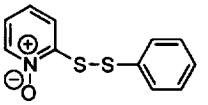
SCHEME 7

TABLE 3. Reaction of Barton PTOC Esters **1a-1f** with Benzenesulfenamides **8e-8g**

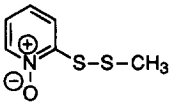
Entry	1	8	3	Time	% Isolated Yield	
					3	4e
1	1a		3a	12h	93	95
2	1b	8e	3b	12h	96	99
3	1c		3c	24h	61	63
4	1a		3d	3 days	77	74
5	1b	8f	3e	7 days	73	76
6	1c		3f	14 days	63	66
7	1d		3j	24h	93	92
8	1e	8g	3k	24h	95	95
9	1f		3l	24h	97	90

The arenesulfenamides **8c-8f** were thermodynamically stable over the span of the concerted reaction and did not significantly disproportionate. The comparatively low yields observed in the toilsome instances (entries 11 and 12 in **Table 2** and entries 3-6 in **Table 3**) were due to a slow rate of reaction and did not result from the decomposition of the reactants. The desired carboxamide and the accompanying unsymmetrical disulfide were easily isolated from relatively clean reaction mixtures - even after extended periods of time (*e.g.* entries 10-12 in **Table 2**).

Our route to carboxamides necessitates the use of a Barton PTOC ester[23] and a sulfenamide[24], both of which are readily available through an assortment of methods. The Barton PTOC ester can either be isolated (especially with the DCC-method) or it can be generated *in situ* and used without considerable decrease in yield[25]. The reaction proceeded in the absence of external catalysis and under neutral conditions which allowed for ease of work-up and purification. Upon completion of the reaction (signaled by the complete consumption of the Barton PTOC ester as determined by TLC), the solvent (usually anhydrous dichloromethane) was removed under aspirator-vacuum and the residue directly subjected to flash column chromatography. In most cases there was sufficient difference in the R_f-values of the carboxamide and the unsymmetrical disulfide to ensure complete separation over silica gel. The unsymmetrical disulfide was formed as the only "by-product". These disulfides are not only synthetically valuable as sulfenylating agents[26], they also possess some value as antimicrobial agents. For example, disulfide **4e** has been patented and is particularly effective against the yeast *Pityrosporum ovale* which is commonly found in the scalp and frequently associated with the dandruff syndrome[27], while disulfide **4f** is a potent seed disinfectant[28].

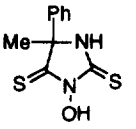


4e

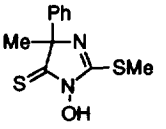


4f

The solvents of choice appear to be either anhydrous dichloromethane or tetrahydrofuran. Polar congeners such as *N,N*-dimethylformamide and 2,2,2-trifluoroethanol proved detrimental to yield. The addition of 5.0 M $LiClO_4$-Et_2O[29] to the demanding cases (*cf.* entry 9 in **Table 2**) did not significantly enhance the reaction rate, neither did labilization of the S-N bond *via* exclusive *S*-atom coordination of the sulfenamide to a low-valent transition metal such as chromium(0)[30]. Selenenamides[31] were also considered as carriers of the amine group. These compounds are, however, difficult to prepare (compared with the corresponding sulfenamides) and their rate of disproportionation in solution rendered them of little synthetic utility to us. As such, they were not investigated further. Finally, the 4,4-disubstituted 1-hydroxyimidazolidine-2,5-dithione **9**[32] and the 4,4-disubstituted 2-methylthio-1-hydroxy-4,5-dihydroimidazole-5-thione **10**[32] were considered as alternatives to the PTOC moiety. These compounds, however, failed to give the desired concerted reaction.

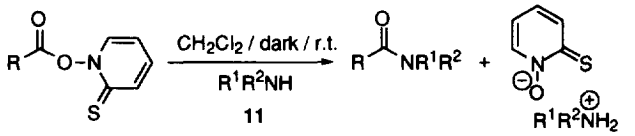


9



10

Barton PTOC Esters and Free Amines. As illustrated in **Scheme 8** and **Table 4**, Barton PTOC esters and primary or secondary amines **11** readily reacted (most probably *via* the well-established tetrahedral mechanism[6]) under mild conditions to give simple carboxamides in good yield (entries 1-7 and 10-12). The reaction did, however, fail in sterically more demanding cases (entries 8 and 9). In the latter two instances, no carboxamide was produced under forcing conditions including, amongst others, a large excess of amine (10 molar equivalents), elevated temperature (reflux) and the presence of an external catalyst (4,4-dimethylaminopyridine, methyl iodide or silver nitrate).



1 **3** **12**

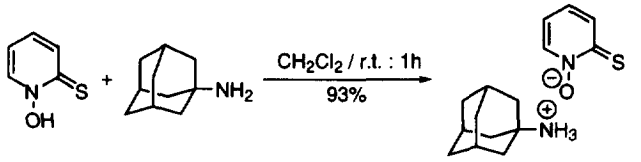
11a R^1 = *n*-Bu, R^2 = H
11b $R^1 = R^2$ = Et
11c $R^1 = R^2$ = ^{i}Pr
11d R^1 = Ph, R^2 = H

SCHEME 8

TABLE 4. Reaction of Barton PTOC Esters **1a-1f** with Selected 1° and 2° Amines

Entry	**1**	**11**	**3**	Time (h)	% Isolated Yield of **3**
1	**1a**		**3g**	1	98
2	**1b**	**11a**	**3h**	1	95
3	**1c**		**3i**	1	92
4	**1a**		**3a**	1	97
5	**1b**	**11b**	**3b**	1	95
6	**1c**		**3c**	12	92
7	**1a**		**3d**	12	96
8	**1b**	**11c**	**3e**	12	---
9	**1c**		**3f**	12	---
10	**1d**		**3j**	12	92
11	**1e**	**11d**	**3k**	6	93
12	**1f**		**3l**	3	93

The only by-product was the acid-base adduct **12**, the identity of which was unambiguously established through the isolation and characterization of the representative acid-base adduct **13** (**Scheme 9**). Adduct **13** is a crystalline salt which gave a satisfactory combustion analysis and, when subjected to a simple aqueous acid-base work-up, released the constituent *N*-hydroxypyridine-2(1*H*)-thione and 1-adamantanamine in yields of 98 and 84% respectively.



13

SCHEME 9

From entries 5 and 6 in **Table 3** and entries 8 and 9 in **Table 4** it is clear that Barton PTOC esters were more reactive towards benzenesulfenamides than towards the corresponding sterically congested free amines. The reaction with non-volatile amines (*e.g.* aniline) demanded an aqueous acid-base work-up whereas the reaction with the corresponding benzenesulfenamides required *only* chromatography to separate the carboxamide and the unsymmetrical disulfide. In cases where steric congestion was absent, however, the reaction with free amines was more convenient since one synthetic step (conversion of the free amine to the corresponding benzenesulfenamide) was eliminated.

In conclusion, we have shown that Barton PTOC esters readily function as activated carboxylic acid derivatives when treated with primary or secondary amines, or with the corresponding sulfenamides. The reaction with sulfenamides is noteworthy since it proceeded under neutral conditions that required minimal work-up and purification. The relatively high yield of sterically demanding carboxamides and biologically important unsymmetrical disulfides has drawn our attention to the construction of dipeptides containing sterically congested amino acid residues. The results of this investigation is disclosed in the article directly following.

EXPERIMENTAL SECTION

General : Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 881 continuous wave spectrophotometer and were taken down neat (thin layer on NaCl) for liquids and oils or as KBr-pellets for crystalline compounds. In all instances air was used as reference. Only selected resonances are reported. ^{1}H and ^{13}C NMR spectra were recorded at 22°C on a Varian XL 200E spectrometer at frequencies of 200 and 50 MHz respectively. Chemical shifts are reported in parts per million (ppm) on the δ-scale and coupling constants (*J*-values) are in Hz. ^{1}H NMR spectra were referenced to tetramethylsilane (δ = 0.00 ppm) while the residual solvent peak was used as an internal reference for ^{13}C NMR spectra. Multiplicities are abbreviated as follows : (br.) s = (broad) singlet, d = doublet, dd = doublet of doublets, t = triplet, tt = triplet of triplets, m = multiplet, q = quartet, qu = quintet. Gas

chromatographic-mass spectroscopic (GC-MS) analyses were performed on a Hewlett-Packard 5890 Series II GC-MS system with a DB5 apolar capillary column interfaced with a 5971 mass selective detector. Ionization was by 70 eV electron impact and masses are reported in units of mass over charge (m/z). The molecular ion is indicated by M^+, the base peak by B^+ and intensities are calculated as a percent of the base peak intensity. Microanalyses were performed by Atlantic Microlab, Inc. of Norcross, Georgia. Analytical thin-layer chromatography (TLC) was performed on glass sheets pre-coated with Merck Kieselgel $60F_{254}$. Flash column chromatography[33] was performed on Baxter S/P® brand silica gel (60Å, 230-400 mesh) for column chromatography. When required, solvents and reagents were dried and purified according to the standard techniques[34].

General Procedure for the Preparation of Barton PTOC Esters **1** : A solution of the required carboxylic acid (5.00 mmol, 1.0 eq.) in anhydrous dichloromethane (25 mL) was added dropwise over a period of 25 minutes to a stirred solution of *N*-hydroxypyridine-2(1*H*)-thione[35] (5.00 mmol, 1.0 eq.) and 1,3-dicyclohexylcarbodiimide (5.10 mmol, 1.02 eq.) in anhydrous dichloromethane (25 mL) at 0°C in the dark (aluminum foil) under an argon atmosphere. The resulting light-yellow mixture was slowly (2h) warmed to ambient temperature and stirred until TLC (hexanes : acetone = 7 : 3 v/v) indicated complete consumption of the thiohydroxamic acid. The mixture was filtered through a short pad (*ca.* 10 cm.) of silica gel (pre-packed with neat dichloromethane) to remove insoluble 1,3-dicyclohexylurea. The filtrate was concentrated under aspirator-vacuum (30 mmHg) at 25°C and the residue was crystallized from dichloromethane / hexanes at -20°C to give the Barton PTOC ester as a crystalline, yellow solid.

N-(3-phenylpropionyloxy)-pyridine-2(1*H*)-thione **1a** : m.p. 130-132°C (dec., lit.[18] : 135°C); IR (KBr) : ν_{max} 3078, 1796, 1594, 1398, 1123 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.66 (dd, 1H, *J* = 1.2 and 8.8 Hz), 7.45-7.11 (m, 7H), 6.74-6.54 (m, 1H), 3.20-2.95 (m, 4H); ^{13}C NMR ($CDCl_3$) : δ 175.6, 168.1, 139.1, 137.5, 137.1, 133.6, 128.6, 128.3, 126.6, 112.6, 33.2, 30.2.

N-(cyclohexylcarbonyloxy)-pyridine-2(1*H*)-thione **1b** : m.p. 110-112°C (dec., lit.[18] : 110°C); IR (KBr) : ν_{max} 2917, 1768, 1589, 1400, 1064 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.65 (d, 1H, *J* = 8.4 Hz), 7.58 (d, 1H, *J* = 7.0 Hz), 7.21 (t, 1H, *J* = 8.4 Hz), 6.65 (t, 1H, *J* = 7.0 Hz), 2.75 (tt, 1H, *J* = 3.5 and 11.1 Hz), 2.35-1.20 (m, 10H); ^{13}C NMR ($CDCl_3$) : δ 175.5, 170.9, 137.6, 137.1, 133.4, 112.5, 40.8, 28.5, 25.2, 24.9.

N-(1-adamantanecarbonyloxy)-pyridine-2(1*H*)-thione **1c** : m.p. 164-165°C (dec., lit.[18] : 166°C); IR (KBr) : ν_{max} 2906, 1772, 1602, 1406, 1123 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.65 (dd, 1H, *J* = 1.8 and 8.8 Hz), 7.51 (dd, 1H, *J* = 1.4 and 7.0 Hz), 7.26-7.12 (m, 1H), 6.70-6.57 (m, 1H), 2.20-2.05 (m, 9H), 1.78 (s, 6H); ^{13}C NMR ($CDCl_3$) : δ 175.7, 172.5, 137.7, 137.3, 133.3, 112.5, 40.8, 38.4, 36.0, 27.5.

N-(4-methoxybenzoyloxy)-pyridine-2(1*H*)-thione **1d**[36] : m.p. 99-101°C (dec.); IR (KBr) : ν_{max} 2999, 1750, 1591, 1246, 1134 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 8.19 (d, 2H, *J* = 8.6 Hz), 7.76-7.64 (m, 2H), 7.30-7.18 (m,

1H), 7.00 (d, 2H, J = 8.6 Hz), 6.73-6.63 (m, 1H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$) : δ 175.9, 164.9, 162.1, 138.1, 137.2, 133.5, 132.9, 117.5, 114.3, 112.6, 55.6.

N-(benzoyloxy)-pyridine-2(1*H*)-thione **1e**[37] : m.p. 93-95°C (dec.); IR (KBr) : ν_{max} 2997, 1741, 1584, 1216, 1126 cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 8.24 (d, 2H, J = 8.4 Hz), 7.77-7.66 (m, 3H), 7.55 (t, 2H, J = 7.6 Hz), 7.30-7.19 (m, 1H), 6.74-6.64 (m, 1H); ^{13}C NMR ($CDCl_3$) : δ 175.9, 162.6, 137.9, 137.3, 134.9, 133.6, 130.7, 128.9, 125.6, 112.7.

N-(4-nitrobenzoyloxy)-pyridine-2(1*H*)-thione **1f**[36] : m.p. 163-165°C (dec.); IR (KBr) : ν_{max} 3057, 1760, 1584, 1216, 1131 cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 8.42 (d, 4H, J = 3.7 Hz), 7.80-7.68 (m, 2H), 7.36-7.23 (m, 1H), 6.79-6.68 (m, 1H); ^{13}C NMR ($CDCl_3$) : δ 175.4, 161.2, 151.4, 137.5, 137.3, 133.8, 131.9, 131.2, 124.0, 112.9.

General Procedure for the Synthesis of Thiobisamines 2 : A solution of freshly purified sulfur dichloride[38] (1.03 g, 10 mmol, 1.0 eq.) in anhydrous ether (10 mL) was added dropwise over a period of 10 minutes to a stirred solution of the appropriate amine (44 mmol, 4.4 eq.) in anhydrous ether (40 mL) at -78°C under an argon atmosphere. The mixture was slowly (12h) warmed to ambient temperature, filtered through Celite® 545 and the filtrate was concentrated under aspirator-vacuum at 30°C. The resulting wine-red liquid was purified by short-path vacuum distillation. The purified thiobisamine was stored in a refrigerator at -20°C under an argon atmosphere.

N,N'-Thiobis(diethyl)-amine **2a** was obtained as a yellow liquid in 83% yield; b.p. 65-67°C / 4 mmHg (lit.[39] : 87.0-87.5°C / 19 mmHg); IR (neat) : ν_{max} 2967, 2935, 1369, 1182, 1012, 891, 630 cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 3.07 (q, 8H, J = 7.1 Hz), 1.14 (t, 12H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) : δ 51.3, 14.3; GC-MS (m/z, %) : 176 (M^+, 40), 104 (B^+), 72 (25).

N,N'-Thiobis(diisopropyl)-amine **2b** was obtained in 78% yield as an unstable orange liquid for which a satisfactory microanalysis could not be obtained; b.p. 63-65°C / 4 mmHg (dec.); IR (neat) : ν_{max} 2971, 2929, 1359, 1180, 1115, 940, 627 cm^{-1}; ^{1}H NMR ($CDCl_3$) : δ 3.46 (qu, 4H, J = 6.7 Hz), 1.12 (d, 24H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) : δ 53.8, 23.4.

General Procedure for the Synthesis of Arenesulfenamides 8 : A solution of the required arenesulfenyl chloride (5.00 mmol, 1.0 eq.) in anhydrous ether (25 mL) was added dropwise over a period of 25 minutes to a stirred solution of the required amine (11.00 mmol, 2.2 eq.) in anhydrous ether (25 mL) at 0°C under an argon atmosphere. The mixture was stirred at 0°C for 1h, filtered through Celite® 545 and the filtrate was concentrated under aspirator-vacuum at 30°C.

N-butyl-*S*-2-nitrobenzenesulfenamide **8a** was obtained in 93% yield after flash column chromatography (hexanes : ether = 9 : 1 v/v, R_f 0.33) as a thick oil which crystallized on standing in a refrigerator at -20°C to give

a crystalline, orange solid, m.p. 27-28°C (lit.[40] : 27-28°C); IR (neat) : ν_{max} 3359, 2928, 1331, 958, 652 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 8.26 (dd, 1H, *J* = 1.3 and 8.3 Hz), 7.96 (dd, 1H, *J* = 1.3 and 8.3 Hz), 7.70-7.58 (m, 1H), 7.30-7.18 (m, 1H), 2.99 (q, 2H, *J* = 6.4 Hz), 2.80-2.64 (m, 1H), 1.70-1.50 (m, 2H), 1.50-1.28 (m, 2H), 0.93 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$) : δ 146.2, 142.5, 133.6, 125.7, 124.3, 124.2, 51.3, 32.7, 19.9, 13.8; GC-MS (m/z, %) : 226 (M^+, 4.8), 106 (24), 77 (B^+).

N,*N*-diethyl-*S*-2-nitrobenzenesulfenamide **8b**[40] was obtained as a wine-red oil in quantitative yield in > 95% purity (as judged by ^1H NMR) and was used without further purification; IR (neat) : ν_{max} 2968, 1330, 1305, 957, 675 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 8.27 (dd, 1H, *J* = 1.4 and 8.3 Hz), 8.02 (dd, 1H, *J* = 1.4 and 8.3 Hz), 7.65-7.54 (m, 1H), 7.29-7.16 (m, 1H), 3.10 (q, 4H, *J* = 7.1 Hz), 1.18 (t, 6H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$) : δ 146.6, 142.2, 133.5, 125.7, 125.1, 124.2, 51.4, 13.5; GC-MS (m/z, %) : 226 (M^+, 19), 161 (61), 106 (B^+).

N,*N*-diethyl-*S*-4-chlorobenzenesulfenamide **8c** was obtained as a colorless oil in quantitative yield in > 95% purity (as judged by ^1H NMR) and was used without further purification; IR (neat) : ν_{max} 2967, 1468, 1374, 1006, 678 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.24 (s, 4H), 2.98 (q, 4H, *J* = 7.1 Hz), 1.16 (t, 6H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$) : δ 140.1, 130.8, 128.6, 125.9, 52.2, 13.6; GC-MS (m/z, %) : 215, 216, 217 (M^+, 62, 8.6, 24), 200, 201, 202 (84, 10, 31), 143, 144, 145 (B^+, 100, 13, 38), 108 (33).

N,*N*-diisopropyl-*S*-4-chlorobenzenesulfenamide **8d**[41] was obtained in 94% yield and crystallized on standing in a refrigerator at -20°C to give a colorless, crystalline solid, m.p. 35-37°C; IR (neat) : ν_{max} 2967, 1465, 1377, 1008, 810 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.20 (s, 4H), 3.37 (qu, 2H, *J* = 6.5 Hz), 1.14 (d, 12H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$) : δ 144.5, 129.3, 128.3, 123.0, 55.6, 22.0; GC-MS (m/z, %) : 243, 244, 245 (M^+, 62, 10, 23), 228, 229, 230 (B^+, 100, 15, 37), 186, 187, 188 (98, 13, 36), 143, 144, 145 (83, 21, 37), 108 (31).

N,*N*-diethylbenzenesulfenamide **8e** was obtained in 75% yield as a colorless oil after short-path distillation under vacuum, b.p. 95-97°C / 4 mmHg (lit.[42] : 90°C / 3.5 mmHg); IR (neat) : ν_{max} 2969, 1473, 1376, 1021, 690 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.36-7.22 (m, 4H), 7.16-7.06 (m, 1H), 2.99 (q, 4H, *J* = 7.1 Hz), 1.18 (t, 6H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$) : δ 141.1, 128.5, 125.3, 125.0, 52.1, 13.7; GC-MS (m/z, %) : 181 (M^+, 33), 166 (62), 109 (B^+).

N,*N*-diisopropylbenzenesulfenamide **8f** was obtained in 79% yield as a colorless oil after short-path distillation under vacuum, b.p. 78-80°C / 1.1 mmHg (lit.[43] : 71-73°C / 0.4 mmHg); IR (neat) : ν_{max} 2970, 1471, 1376, 1022, 691 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.37-7.17 (m, 4H), 7.07-6.97 (m, 1H), 3.38 (qu, 2H, *J* = 6.5 Hz), 1.16 (d, 12H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$) : δ 145.8, 128.2, 123.9, 121.7, 55.5, 22.1; GC-MS (m/z, %) : 209 (M^+, 72), 194 (B^+), 152 (98), 109 (62).

Benzenesulfenanilide **8g** was obtained in 97% yield as a colorless, crystalline solid after flash column chromatography (hexanes : acetone = 9 : 1 v/v, R_f 0.40), m.p. 53-55°C (lit.[44] : 53-55°C); IR (KBr) : ν_{max} 3356,

1464, 1224, 907, 682 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.36-6.80 (m, 10H), 5.26-4.98 (br. s, 1H); ^{13}C NMR ($CDCl_3$) : δ 146.6, 141.4, 129.3, 128.9, 125.4, 122.4, 120.5, 114.6; GC-MS (m/z, %) : 201 (M^+, B^+), 92 (50), 65 (24).

The sulfenamides **8a** and **8b** were obtained from commercially available 2-nitrobenzenesulfenyl chloride and the appropriate amine. **8c** and **8d** were similarly prepared from 4-chlorobenzenesulfenyl chloride, while **8e**, **8f** and **8g** were derived from benzenesulfenyl chloride. The latter two sulfenyl chlorides were prepared according to the method of Harpp[45].

General Procedure for the Reaction Between Barton PTOC Esters 1 and Thiobisamines 2 or Arenesulfenamides 8 : A solution of the appropriate sulfenamide **2** or **8** (1.05 mmol, 1.05 eq.) in anhydrous dichloromethane (2.5 mL) was added dropwise over a period of 5 minutes to a stirred solution of the required Barton PTOC ester (1.00 mmol, 1.0 eq.) in anhydrous dichloromethane (2.5 mL) at ambient temperature in the dark (aluminum foil) under an argon atmosphere. The mixture was stirred until TLC (hexanes : acetone = 7 / 3 v/v) indicated complete consumption of the Barton PTOC ester (which gives a characteristic yellow spot readily visible with the naked eye, UV or I_2 / SiO_2). The volatiles were removed under aspirator-vacuum at 30°C and the residue was flash-chromatographed over silica gel. The carboxamide **3** was eluted first (hexanes : acetone = 8 : 2 v/v), while subsequent elution with hexanes : acetone = 6 : 4 v/v afforded the unsymmetrical disulfide **4**. The carboxamides **3** were visualized with I_2 / SiO_2, while the unsymmetrical disulfides **4** absorb intensely at *ca.* 275 nm under UV-light.

Carboxamides **3** :

N,N-diethylbenzenepropanamide **3a** was obtained as a light-yellow liquid, b.p. 155-157°C / 5 mmHg (lit.[46] : 170°C / 11 mmHg); IR (neat) : ν_{max} 2970, 1638, 1449, 1378, 1266 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.35-7.13 (m, 5H), 3.37 (q, 2H, *J* = 7.1 Hz), 3.21 (q, 2H, *J* = 7.1 Hz), 2.99 (t, 2H, *J* = 7.4 Hz), 2.59 (t, 2H, *J* = 7.4 Hz), 1.11 (t, 3H, *J* = 7.1 Hz), 1.09 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$) : δ 171.1, 141.5, 128.3, 125.9, 41.8, 40.1, 35.0, 31.5, 14.2, 13.0; GC-MS (m/z, %) : 205 (M^+, 75), 91 (68), 58 (B^+).

N,N-diethylcyclohexanecarboxamide **3b** was obtained as a light-yellow liquid, b.p. 93-94°C / 0.1 mmHg (lit.[47] : 94-95°C / 0.1 mmHg); IR (neat) : ν_{max} 2936, 1623, 1449, 1377, 1261 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 3.34 (q, 4H, *J* = 7.2 Hz), 2.41 (tt, 1H, *J* = 3.6 and 11.1 Hz), 1.90-1.03 (m, 16H); ^{13}C NMR ($CDCl_3$) : δ 175.3, 41.5, 40.6, 39.8, 29.5, 25.75, 25.68, 14.9, 13.0; GC-MS (m/z, %) : 183 (M^+, 65), 128 (B^+), 83 (62).

N,N-diethyl-1-adamantanecarboxamide **3c** was obtained as a colorless, crystalline solid, m.p. 66-68°C (lit.[48] : 66-67°C); IR (KBr) : ν_{max} 2909, 1608, 1406, 1373, 1270 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 3.43 (q, 4H, *J* = 7.0 Hz), 2.00 (s, 9H), 1.72 (s, 6H), 1.13 (t, 6H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) : δ 175.8, 41.7, 41.6, 39.0, 36.5, 28.4, 13.5; GC-MS (m/z, %) : 235 (M^+, 32), 135 (B^+), 79 (14).

N,N-diisopropylbenzenepropanamide **3d** was obtained as a colorless oil, b.p. 156°C / 0.4 mmHg (lit.[49] : 170°C / 0.8 mmHg); IR (neat) : ν_{max} 2966, 1633, 1440, 1369, 1318 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.36-7.12 (m, 5H), 3.91 (qu, 1H, *J* = 6.7 Hz), 3.62-3.26 (m, 1H), 2.96 (t, 2H, *J* = 8.0 Hz), 2.58 (t, 2H, *J* = 8.0 Hz), 1.39 (d, 6H, *J* = 6.7 Hz), 1.12 (d, 6H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$) : δ 170.8, 141.6, 128.4, 128.3, 125.9, 48.1, 45.5, 37.0, 31.5, 20.8, 20.6; GC-MS (m/z, %) : 233 (M^+, 59), 105 (56), 86 (B^+).

N,N-diisopropylcyclohexanecarboxamide **3e** was obtained as a colorless, crystalline solid, m.p. 75-76°C (lit.[50] : 74-75°C); IR (KBr) : ν_{max} 2926, 1610, 1432, 1320, 1279 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 3.98 (qu, 1H, *J* = 6.7 Hz), 3.76-3.38 (m, 1H), 2.37 (tt, 1H, *J* = 3.5 and 11.1 Hz), 1.90-1.40 (m, 10H), 1.34 (d, 6H, *J* = 6.9 Hz), 1.22 (d, 6H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$) : δ 175.2, 47.3, 45.3, 42.4, 29.5, 25.9, 25.8, 21.4, 20.7; GC-MS (m/z, %) : 211 (M^+, 20), 168 (61), 86 (B^+).

N,N-diisopropyl-1-adamantanecarboxamide **3f** was obtained as a colorless, crystalline solid, m.p. 143-144°C (lit.[51] : 147-149°C); IR (KBr) : ν_{max} 2904, 1605, 1437, 1362, 1295 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 4.75-4.35 (br. s, 1H), 3.45-3.05 (br. s, 1H), 2.10-1.88 (m, 9H), 1.72 (s, 6H), 1.52-1.02 (m, 12H); ^{13}C NMR ($CDCl_3$) : δ 183.5, 175.6, 42.3, 40.4, 38.9, 38.5, 36.7, 36.4, 28.6, 27.8, 20.7; GC-MS (m/z, %) : 263 (M^+, 7.7), 220 (71), 135 (B^+).

N-butylbenzenepropanamide **3g** was obtained as a light-yellow oil, b.p. 159-161°C / 0.4 mmHg (lit.[52] : 145-147°C / 0.1 mmHg); IR (neat) : ν_{max} 3295, 2959, 1640, 1545, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 7.34-7.12 (m, 5H), 6.10-5.40 (m, 1H), 3.19 (q, 2H, *J* = 6.7 Hz), 2.95 (t, 2H, *J* = 7.7 Hz), 2.45 (t, 2H, *J* = 7.7 Hz), 1.49-1.14 (m, 4H), 0.88 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$) : δ 172.0, 140.9, 128.4, 128.2, 126.1, 39.1, 38.44, 38.36, 31.7, 31.5, 19.9, 13.7; GC-MS (m/z, %) : 205 (M^+, B^+), 105 (78), 91 (87).

N-butylcyclohexanecarboxamide **3h** was obtained as a colorless, crystalline solid, m.p. 65-67°C (lit.[53] : 59-62°C); IR (KBr) : ν_{max} 3299, 2929, 1633, 1539, 1437 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 6.06-5.62 (br. s, 1H), 3.24 (q, 2H, *J* = 6.6 Hz), 2.18-1.98 (m, 1H), 1.95-1.03 (m, 14H), 0.92 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$) : δ 176.0, 45.5, 38.9, 31.7, 29.6, 25.7, 20.0, 13.7; GC-MS (m/z, %) : 183 (M^+, 47), 128 (B^+), 83 (88).

N-butyl-1-adamantanecarboxamide **3i** was obtained as a colorless, crystalline solid, m.p. 92-94°C; IR (KBr) : ν_{max} 3311, 2903, 1624, 1539, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 5.86-5.46 (br. s, 1H), 3.23 (q, 2H, *J* = 6.7 Hz), 2.15-1.60 (m, 15H), 1.57-1.22 (m, 4H), 0.92 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$) : δ 177.7, 40.4, 39.2, 38.9, 36.4, 31.6, 28.1, 20.0, 13.7; GC-MS (m/z, %) : 235 (M^+, 16), 193 (36), 135 (B^+); Anal. Calc. for $C_{15}H_{25}NO$: C 76.55, H 10.71, N 5.95. Found : C 76.45, H 10.67, N 5.98.

p-Anisanilide **3j** was obtained as a colorless, crystalline solid, m.p. 169-171°C (lit.[54] : 168-169°C); IR (KBr) : ν_{max} 3335, 1647, 1501, 1238, 1175 cm^{-1}; ^1H NMR (DMSO) : δ 10.07 (s, 1H), 7.94 (d, 2H, *J* = 7.8 Hz), 7.75 (d, 2H, *J* = 7.8 Hz), 7.32 (t, 2H, *J* = 7.6 Hz), 7.13-7.00 (m, 3H), 3.81 (s, 3H); ^{13}C NMR (DMSO) : δ 164.9,

161.9, 139.3, 129.6, 128.6, 127.0, 123.4, 120.3, 113.6, 55.4; GC-MS (m/z, %) : 227 (M^+, 23), 135 (B^+), 77 (8.8).

Benzanilide **3k** was obtained as a colorless, crystalline solid, m.p. 162-164°C (lit.[55] : 160.8°C); IR (KBr) : ν_{max} 3327, 1635, 1505, 1425, 1310 cm^{-1}; ^1H NMR (DMSO) : δ 10.24 (s, 1H), 7.94 (d, 2H, J = 7.1 Hz), 7.77 (d, 2H, J = 8.0 Hz), 7.64-7.46 (m, 3H), 7.34 (t, 2H, J = 7.8 Hz), 7.09 (t, 1H, J = 7.3 Hz); ^{13}C NMR (DMSO) : δ 165.6, 139.2, 135.0, 131.6, 128.6, 128.4, 127.7, 123.7, 120.4; GC-MS (m/z, %) : 197 (M^+, 46), 105 (B^+), 77 (34).

4-Nitrobenzanilide **3l** was obtained as a colorless, crystalline solid, m.p. 217-219°C (lit.[56] : 217.5-218.5°C); IR (KBr) : ν_{max} 3306, 1632, 1500, 1426, 1310 cm^{-1}; ^1H NMR (DMSO) : δ 10.55 (s, 1H), 8.35 (d, 2H, J = 8.7 Hz), 8.16 (d, 2H, J = 8.7 Hz), 7.76 (d, 2H, J = 7.7 Hz), 7.36 (t, 2H, J = 7.7 Hz), 7.12 (t, 1H, J = 7.3 Hz), 3.81 (s, 3H); ^{13}C NMR (DMSO) : δ 163.9, 149.1, 140.6, 138.7, 129.2, 128.7, 124.2, 123.6, 120.5; GC-MS (m/z, %) : 242 (M^+, 62), 150 (B^+), 120 (32).

Unsymmetrical Disulfides **4** :

2-(*N*,*N*-diethylaminodithio)-pyridine-*N*-oxide **4a** was obtained as an unstable yellow oil for which a satisfactory microanalysis could not be obtained; IR (neat) : ν_{max} 2965, 1453, 1253, 904, 760 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 8.24 (dd, 1H, J = 0.7 and 6.4 Hz), 8.10 (dd, 1H, J = 1.7 and 8.2 Hz), 7.36-7.22 (m, 1H), 7.18-7.04 (m, 1H), 2.93 (q, 4H, J = 7.1 Hz), 1.16 (t, 6H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$) : δ 152.2, 138.9, 125.3, 123.7, 121.8, 51.4, 13.1.

2-(*N*,*N*-diisopropylaminodithio)-pyridine-*N*-oxide **4b** was obtained as a colorless, crystalline solid, m.p. 98-99°C (dec.); IR (KBr) : ν_{max} 2953, 1393, 1221, 959, 761 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 8.25 (dd, 1H, J = 0.7 and 6.5 Hz), 8.15 (dd, 1H, J = 1.5 and 8.3 Hz), 7.40-7.27 (m, 1H), 7.16-7.03 (m, 1H), 3.43 (qu, 2H, J = 6.6 Hz), 1.16 (d, 12H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) : δ 152.9, 138.9, 125.3, 123.9, 121.3, 56.9, 22.1; Anal. Calc. for $C_{11}H_{18}N_2OS_2$: C 51.13, H 7.02, N 10.84, S 24.82. Found : C 51.24, H 7.06, N 10.75, S 24.75.

2-(2'-Nitrophenyldithio)-pyridine-*N*-oxide **4c** was obtained as a crystalline, yellow solid, m.p. 176-177°C (dec.); IR (KBr) : ν_{max} 2930, 1327, 1215, 1095, 733 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 8.41-8.27 (m, 2H), 7.90 (dd, 1H, J = 0.9 and 8.2 Hz), 7.67-7.50 (m, 2H), 7.48-7.36 (m, 1H), 7.34-7.14 (m, 2H); ^{13}C NMR ($CDCl_3$) : δ 149.5, 146.0, 138.7, 134.6, 134.2, 127.1, 127.0, 126.5, 126.3, 122.5, 121.8; Anal. Calc. for $C_{11}H_8N_2O_3S_2$: C 47.13, H 2.88, N 9.99, S 22.87. Found : C 47.17, H 2.90, N 9.91, S 22.81.

2-(4'-Chlorophenyldithio)-pyridine-*N*-oxide **4d** was obtained as a colorless, crystalline solid, m.p. 131-133°C (dec.; lit.[27] : 133.5-137.5°C); IR (KBr) : ν_{max} 3064, 1453, 1247, 1083, 808 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 8.25 (d, 1H, J = 6.3 Hz), 7.73 (dd, 1H, J = 1.4 and 8.2 Hz), 7.48-7.10 (m, 6H); ^{13}C NMR ($CDCl_3$) : δ 150.6, 138.4,

133.6, 132.7, 129.3, 128.9, 126.3, 122.1, 121.5; GC-MS (m/z, %) : 278, 279, 280 (M^+, 29, 4.4, 13), 220, 221, 222 (B^+, 100, 14, 10), 156 (63).

2-(Phenyldithio)-pyridine-*N*-oxide **4e** was obtained as a colorless, crystalline solid on standing in a refrigerator at -20°C, m.p. 79-81°C (dec.; lit.[27] : 82.1-82.2°C); IR (neat) : ν_{max} 2925, 1462, 1248, 1135, 686 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 8.24 (d, 1H, *J* = 6.1 Hz), 7.78 (dd, 1H, *J* = 1.9 and 8.2 Hz), 7.49 (dd, 1H, *J* = 1.6 and 8.1 Hz), 7.38-7.19 (m, 4H), 7.19-7.08 (m, 1H); ^{13}C NMR ($CDCl_3$) : δ 151.3, 138.5, 134.3, 129.3, 127.7, 127.6, 126.3, 121.9, 121.8.

Hydrazine derivative **5** : DEAD (3.9 mL, 25.0 mmol, 25.0 eq.) was added dropwise over a period of 5 minutes to a stirred solution of the Barton PTOC ester **1b** (237 mg, 1.0 mmol, 1.0 eq.) and distilled water (180 µL, 10.0 mmol, 10.0 eq.) in anhydrous THF (5 mL) at ambient temperature in the dark (aluminum foil) under an argon atmosphere. The orange mixture was stirred at ambient temperature for 1h. The volatiles were removed under aspirator-vacuum at 30°C and the residue was flash-chromatographed (hexanes : acetone = 5 : 5 v/v) to give a mixture of cyclohexanecarboxylic acid **6** and excess DEAD (both at R_f 0.90) and the pure hydrazine derivative **5** (205 mg, 0.68 mmol, 68%) at R_f 0.25 as a colorless, crystalline solid, m.p. 70-72°C (dec.); IR (KBr) : ν_{max} 2980, 1723, 1465, 1298, 1231, 1043 cm^{-1}; ^1H NMR ($CDCl_3$) : δ 8.18 (d, 1H, *J* = 6.4 Hz), 7.88-7.62 (br. s, 2H), 7.46-7.34 (m, 1H), 7.21-7.09 (m, 1H), 4.27 (q, 2H, *J* = 7.1 Hz), 4.20 (q, 2H, *J* = 7.1 Hz), 1.27 (t, 6H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$) : δ 156.3 and 156.0, 152.6, 137.5, 127.7, 121.4, 121.0, 64.5 and 62.1, 14.3 and 14.2; Anal. Calc. for $C_{11}H_{15}N_3O_5S$: C 43.85, H 5.02, N 13.95, S 10.64. Found : C 43.71, H 5.08, N 13.74, S 10.52.

The mixture containing cyclohexanecarboxylic acid **6** and excess DEAD was taken up in dichloromethane (25 mL) and extracted with ice-cold 0.1 M NaOH (3 x 25 mL). The combined aqueous layers were extracted with ether (3 x 25 mL), acidified to *ca.* pH 2 with 0.1 M HCl, saturated with NaCl and re-extracted with ethyl acetate (3 x 25 mL). The combined ethyl acetate layers were dried over Na_2SO_4, filtered and concentrated under aspirator-vacuum at 30°C to give cyclohexanecarboxylic acid **6** (93 mg, 0.73 mmol, 73%) as a single spot by TLC and pure by ^1H NMR.

General Procedure for the Reaction Between Barton PTOC Esters 1 and Primary or Secondary Amines 11 : A solution of the amine **11** (2.50 mmol, 2.5 eq.) in anhydrous dichloromethane (2.5 mL) was added dropwise over a period of 5 minutes to a stirred solution of the required Barton PTOC ester **1** (1.00 mmol, 1.0 eq.) in anhydrous dichloromethane (2.5 mL) at ambient temperature in the dark (aluminum foil) under an argon atmosphere. The mixture was stirred until TLC (hexanes : acetone = 7 : 3 v/v) indicated complete consumption of the Barton PTOC ester. The volatiles were removed under aspirator-vacuum at 30°C. The residue was taken up in ethyl acetate (20 mL) and successively washed with 5% m/v aqueous $KHSO_4$ (3 x 5 mL), brine (5 mL), 5% m/v aqueous $NaHCO_3$ (3 x 5 mL) and again with brine (5 mL). The organic phase was dried over Na_2SO_4, filtered, concentrated and flash-chromatographed (hexanes : acetone = 8 : 2 v/v) to give the desired carboxamide **3** as a single spot by TLC and pure by NMR.

Acid-base adduct **13** : A solution of *N*-hydroxypyridine-2(1*H*)-thione (318 mg, 2.50 mmol, 1.0 eq.) in anhydrous dichloromethane (10 mL) was added dropwise over a period of 10 minutes to a stirred solution of 1-adamantanamine (378 mg, 2.50 mmol, 1.0 eq.) in anhydrous dichloromethane (10 mL) at ambient temperature under an argon atmosphere. The resulting snow-white suspension was stirred at ambient temperature for 1h and the volatiles were removed under aspirator-vacuum at 30°C. The residue was triturated with anhydrous ether (50 mL), chilled in a refrigerator at -20°C for 1h and filtered. The white precipitate was washed with anhydrous ether (3 x 20 mL), collected and recrystallized from 2-propanol to give **13** (649 mg, 2.33 mmol, 93%) as colorless needles, m.p. 176-178°C; IR (KBr) : ν_{max} 2913, 1502, 1443, 1136, 747 cm^{-1}; ^1H NMR (CD_3OD) : δ 8.02 (d, 1H, *J* = 6.4 Hz), 7.55 (d, 1H, *J* = 8.3 Hz), 6.99 (t, 1H, *J* = 8.3 Hz), 6.74 (t, 1H, *J* = 6.4 Hz), 2.12, 1.88 and 1.71 (3 x s, 15H); ^{13}C NMR (CD_3OD) : δ 168.2, 139.7, 133.9, 128.1, 116.6, 52.5, 41.6, 36.5, 30.4; Anal. Calc. for $C_{15}H_{22}N_2OS$: C 64.71, H 7.96, N 10.06, S 11.52. Found : C 64.56, H 7.99, N 10.16, S 11.44.

Acknowledgments : We thank the Welch Foundation, the Schering-Plough Corporation and the N.I.H. for the support of this work. We also thank the Olin Corporation (Dr. R. Hani) for generous gifts of "Sodium Omadine®". Prof. Andrzej Sobkowiak is gratefully acknowledged for the translation of articles from Polish and Russian. We thank Richard ("Hakeem") Vonder Embse for helpful discussion.

REFERENCES AND NOTES

1. Barton, D. H. R., Crich, D., Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1983**, 939-941; *Idem, Tetrahedron* **1985**, *41*, 3901-3924.

2. Prof. Martin Newcomb coined PTOC as the acronym for the Pyridine-2-Thione-*N*-OxyCarbonyl moiety : Newcomb, M. *Tetrahedron* **1993**, *49*, 1151-1176.

3. See, for example : Barton, D. H. R., Jaszberenyi, J. Cs., Theodorakis, E. A., Reibenspies, J. H. *J. Am. Chem. Soc.* **1993**, *115*, 8050-8059 and the many references there cited.

4. Paquette, L. A. *J Am. Chem. Soc.* **1965**, *87*, 5186-5190; Taylor, E. C., Kienzle, F., McKillop, A. *J. Org. Chem.* **1970**, *35*, 1672-1674.

5. For a recent example, see : Kim, H.-O., Gardner, B., Kahn, M. *Tetrahedron Lett.* **1995**, *36*, 6013-6016.

6. Beckwith, A. L. J. in "*The Chemistry of Amides*", Ed. J. Zabicky, Interscience Publishers (London), 1970, Chapter 2, pp. 73-185; Challis, B. C. and Challis, J. A. in "*Comprehensive Organic Chemistry*", Eds. D. H. R. Barton and W. D. Ollis, Pergamon Press (Oxford), 1979, Volume 2, Chapter 9.9, pp. 957-986.

7. Coste, J., Frérot, E., Jouin, P. *Tetrahedron Lett.* **1991**, *32*, 1967-1970 and references there cited; Wijkmans, J. C. H. M., Blok, F. A. A., Van der Marel, G. A., Van Boom, J. H., Bloemhoff, W. *Ibid.* **1995**, *36*, 4643-4646.

8. White, D. J. G. (Ed.), "*Cyclosporin A. Proceedings of an International Conference on Cyclosporin A*", Elsevier Biomedical Press (Amsterdam), 1982.

9. Wenschuh, H., Beyermann, M., Krause, E., Brudel, M., Winter, R., Schümann, M., Carpino, L. A., Bienert, M. *J. Org. Chem.* **1994**, *59*, 3275-3280 and references there cited.

10. Schmitt, H., Jung, G. *Liebigs Ann. Chem.* **1985**, 321-344.

11. Knapp, S. *Chem. Rev.* **1995**, *95*, 1859-1876.

12. De Almeida, M. V., Barton, D. H. R., Bytheway, I., Ferreira, J. A., Hall, M. B., Liu, W., Taylor, D. K., Thomson, L. *J. Am. Chem. Soc.* **1995**, *117*, 4870-4874.

13. Bowman, W. R., Clark, D. N., Marmon, R. J. *Tetrahedron* **1994**, *50*, 1275-1294 and references there cited.

14. Ueki, M., Maruyama, H., Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1108-1111.

15. Parfenov, É. A., Fomin, V. A. *J. Gen. Chem. USSR (Engl. Transl.)* **1981**, *51*, 961-968.

16. *Ibid.* **1981**, *51*, 947-953.

17. Davis, F. A. *Int. J. Sulfur Chem.* **1973**, *8*, 71-81.

18. Barton, D. H. R., Ozbalik, N., Vacher, B. *Tetrahedron* **1988**, *44*, 7385-7392.

19. This augurs well for a non-radical mechanism. It should, however, be noted that radical processes can be triggered by means other than heating or irradiation (for an example of a radical reaction catalyzed by oxygen, see : Barton, D. H. R., Bridon, D., Zard, S. Z. *Tetrahedron Lett.* **1986**, *27*, 4309-4312). We did, of course, verify that a radical trap (TEMPO) does not influence the distribution of products under the standard reaction conditions (*cf.* Experimental Section).

20. Cotton, F. A., Wilkinson, G., "*Advanced Inorganic Chemistry*", John Wiley & Sons (New York), Fifth Edition, 1988, Chapter 13, pp. 491-493.

21. See, also : Tavs, P. *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 1048-1049 and Davis, F. A., Skibo, E. B. *J. Org. Chem.* **1976**, *41*, 1333-1336.

22. Díaz, C., Cuevas, J., González, G. *Sulfur Letters* **1990**, *11*, 145-155.

23. Barton, D. H. R., Samadi, M. *Tetrahedron* **1992**, *48*, 7083-7090; For a recent article on the use of the thallium(I) salt of *N*-hydroxypyridine-2(1*H*)-thione, see : Aveline, B. M., Kochevar, I. E., Redmond, R. W. *J. Am. Chem. Soc.* **1995**, *117*, 9699-9708.

24. Craine, L., Raban, M. *Chem. Rev.* **1989**, *89*, 689-712; Petrov, K. A., Rudnev, G. V., Sorokin, V. D. *Russ. Chem. Rev.* **1990**, *59*, 1431-1452.

25. We prefer our method involving the use of 2,2'-dithiodipyridine-1,1'-dioxide and a tervalent phosphine for the generation of transient Barton PTOC esters (see the article directly following).

26. Barton, D. H. R., Chen, C., Wall, G. M. *Tetrahedron* **1991**, *47*, 6127-6138.

27. Douglass, M. L., U.S. Patent 4, 049, 665, *Chem. Abstr.* **1978**, *88*, 6743f.

28. Nakayama, K., Yoshio, H., Yamashita, N., Jpn. Kokai Tokkyo Koho JP 61 56, 104, *Chem. Abstr.* **1986**, *105*, 74387q.

29. Grieco, P. A. *Aldrichimica Acta* **1991**, *24*, 59-66.

30. Díaz, C., Cuevas, J., González, G. *Z. Anorg. Allg. Chem.* **1991**, *592*, 7-16.

31. Irgolic, K. and Kudchadker, M. V. in "*Selenium*", Eds. R. A. Zingaro and W. Cooper, Van Nostrand Reinhold (New York), 1974, Chapter 8, pp. 408-545.

32. Barton, D. H. R., Tachdjian, C. *Tetrahedron* **1992**, *48*, 7091-7108.

33. Still, W. C., Kahn, M., Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

34. Perrin, D. D., Armarego, W. L. F., Perrin, D. R., "*Purification of Laboratory Chemicals*", Pergamon Press (Oxford), Second Edition, 1980.

35. *N*-Hydroxypyridine-2(1*H*)-thione can be purchased as the sodium salt "Sodium Omadine®" from the Olin Corporation. The free acid is readily obtained on acidification with HCl : Shaw, E., Bernstein, J., Losee, K., Lott, W. A. *J. Am. Chem. Soc.* **1950**, *72*, 4362-4364; See also : Barton, D. H. R., Bridon, D., Fernandez-Picot, I., Zard, S. Z. *Tetrahedron* **1987**, *43*, 2733-2740.

36. Barton, D. H. R., Lacher, B., Zard, S. Z. *Tetrahedron Lett.* **1985**, *26*, 5939-5942.

37. Barton, D. H. R., Ramesh, M. *Ibid.* **1990**, *31*, 949-952.

38. In our hands, sulfur dichloride was best purified by the method of Harpp : Harpp, D. N., Steliou, K., Chan, T. H. *J. Am. Chem. Soc.* **1978**, *100*, 1222-1228.

39. Lengfeld, F., Stieglitz, J. *Chem. Ber.* **1895**, *28*, 575-576.

40. Billman, J. H., O'Mahony, E. *J. Am. Chem. Soc.* **1939**, *61*, 2340-2341.

41. Raban, M., Yamamoto, G. *Ibid.* **1979**, *101*, 5890-5895.

42. Lecher, H., Holschneider, F. *Chem. Ber.* **1924**, *57*, 755-758.

43. Davis, F. A., Friedman, A. J., Kluger, E. W., Skibo, E. B., Fretz, E. R., Milicia, A. P., LeMasters, W. C., Bentley, M. D., Lacadie, J. A., Douglass, I. B. *J. Org. Chem.* **1977**, *42*, 967-972.

44. Lecher, H., Holschneider, F., Köberle, K., Speer, W., Stöcklin, P. *Chem. Ber.* **1925**, *58*, 409-416.

45. Harpp, D. N., Friedlander, B. T., Smith, R. A. *Synthesis* **1979**, 181-182.

46. Richter, F. (Ed.), "*Beilstein's Handbuch der Organischen Chemie*", Springer-Verlag (Berlin), 1949, Second Work, Vol. 9, p. 340.

47. Lynn, J. W., English, J. *J. Am. Chem. Soc.* **1951**, *73*, 4284-4286.

48. Danilenko, G. I., Vladimirtsev, I. F., Yurchenko, A. G., Galegov, G. A., Leont'eva, N. O., Isaev, S. D., Dikolenko, E. I., Boldyrev, I. V., Yurchenko, R. I., Kotenko, S. I. *Farm. Zh. (Kiev)* **1976**, 36-40.

49. Adam, W., Metz, M., Prechtl, F., Renz, M. *Synthesis* **1994**, 563-566.

50. Krapcho, A. P., Kashdan, D. S., Jahngen, E. G. E., Lovey, A. J. *J. Org. Chem.* **1977**, *42*, 1189-1194.

51. Lempke, T., Cessak, M. *Acta Polon. Pharm.* **1986**, *43*, 637-638.

52. Seymour, S. L., Parrino, V. A., Freedman, L. *J. Am. Chem. Soc.* **1959**, *81*, 3728-3736.

53. Markó, I. E., Mekhalfia, A. *Tetrahedron Lett.* **1990**, *31*, 7237-7240.

54. Leuckart, R., Schmidt, M. *Chem. Ber.* **1885**, *18*, 2338-2341.

55 Vanstone, E. *J. Chem. Soc.* **1913**, *103*, 1826-1838.

56. Lockemann, G. *Chem. Ber.* **1942**, *75*, 1911-1921.

(*Received in USA* 29 *March* 1996; *revised* 16 *May* 1996; *accepted* 17 *May* 1996)