3-Acetylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (10). A solution of **4** (98 mg, 1 mmol) and cyclopentadiene (132 mg, 2 mmol) was stirred in benzene (2 mL) at room temperature for 30 min. After evaporation of the solvent, **10** was obtained nearly quantitatively as a ca. 1:1 endo and exo mixture of stereoisomers: IR 2720, 1710 cm^{-1}; ^1H NMR δ 1.26–1.55 (m, 2 H), 2.18 and 2.26 (s, each 1.5 H), 2.85–3.50 (m, 4 H), 6.02–6.31 (m, 2 H), 9.58 and 9.83 (s, each 0.5 H). Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.20; H, 7.35.

Registry No. **4**, 34218-21-8; **5**, 129492-01-9; **6** (R = H), 4401-11-0; **7** (R = H), 129492-02-0; **8**, 719-00-6; **9**, 129492-03-1; **10** (isomer 1), 129568-34-9; **10** (isomer 2), 129568-35-0; *endo*-**11**, 129492-04-2; *exo*-**11**, 129492-12-2; *endo*-**12**, 129492-05-3; *endo*-**13**, 129492-06-4; *exo*-**13**, 129492-13-3; *endo*-**14**, 129492-07-5; *exo*-**14**, 129492-14-4; **15**, 129492-08-6; *endo*-**16**, 129492-09-7; *exo*-**16**, 129492-15-5; *endo*-**17**, 129492-10-0; *exo*-**17**, 129492-16-6; **18**, 129492-11-1; TMSOTf, 27607-77-8; $SnCl_4$, 7646-78-8; $TiCl_4$, 7550-45-0; cyclopentadiene, 542-92-7; furan, 110-00-9.

A New Route to N-Monosubstituted Thioamides Utilizing Phosphoramidothionates as Reagents for the Thioamidation of Carboxylic Acids

Kenneth E. DeBruin* and Eric E. Boros

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

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Several *N*-monosubstituted thioamides have been synthesized from the corresponding carboxylic acid chlorides and primary amines by a new procedure. The procedure utilizes a commercially available and inexpensive organophosphorus reagent (dimethyl chlorothiophosphate) to derivatize the amine, form the carboxamide bond, and accomplish the thionation of the carbonyl by an intramolecular rearrangement. The phosphoryl group is then cleaved from the resulting thiocarbonyl phosphoryl mixed imide by a simple hydrolysis. Thioamides (RCSNHR′) containing a variety of functionality (R = simple alkyl, phenyl, bulky alkyl, cycloalkylalkyl, α,β-unsaturated, and alkyl with remote keto, ester, or amide carbonyl groups; R′ = methyl, benzyl, allyl) have been prepared by this method in generally high overall yields (50–80%). Competing thionation of remote carbonyl groups or epimerization of a chiral center containing a proton α to a ketone group was not observed.

Introduction

In addition to their wide use in agriculture, medicine, etc., thioamides (thiocarboxamides) undergo an assortment of chemical transformations[1] which make them attractive for synthetic applications. Recent papers have reported new methods for their oxidation to carbonyl compounds,[2] reduction to amines,[3] and conversions to nitriles,[4] thioimidates,[5] and amidines.[6] Numerous heterocycles have been generated by virtue of the dipolar nature of thioamides.[7] Other cyclization reactions have utilized electrophile-induced addition to olefins,[8] photochemistry,[9] and a novel trimethyl phosphite induced addition to an α-diketone.[10] Thioenolate anions of thioamides have been employed in a variety of condensation reactions[11] and stereoselective Michael additions to α,β-unsaturated ketones.[12]

A number of methods for the synthesis of thioamides have been reported.[1,13] Recently, N-substituted thioamides have been prepared from aliphatic ketones (extended Willgerodt–Kindler reaction),[14] nitroacetamides,[15] imine oxides,[16] α-keto acids,[17] orthoformates,[18] dimethyl thioformamide,[19] and unsubstituted thioamides.[20] From carboxylic acids, thioamides are most commonly generated by forming a carboxamide (via the acid chloride) and then treating with thionation agents such as phosphorus pentasulfide or Lawesson's reagent.[21] Treating acid chlorides with Lawesson's reagent followed by addition of an amine has also been described.[22]

We would like to report an alternative procedure for the synthesis of thioamides from carboxylic acids (via acid chlorides) and amines. The procedure utilizes a readily available phosphorochloridothionate reagent to derivatize the amine, form the carboxamide bond, and accomplish the thionation of the carbonyl by an *intramolecular* rearrangement. The resulting phosphoryl group is then cleaved by a simple hydrolysis. Scheme I shows the general pathway. The procedure uses rather mild conditions and

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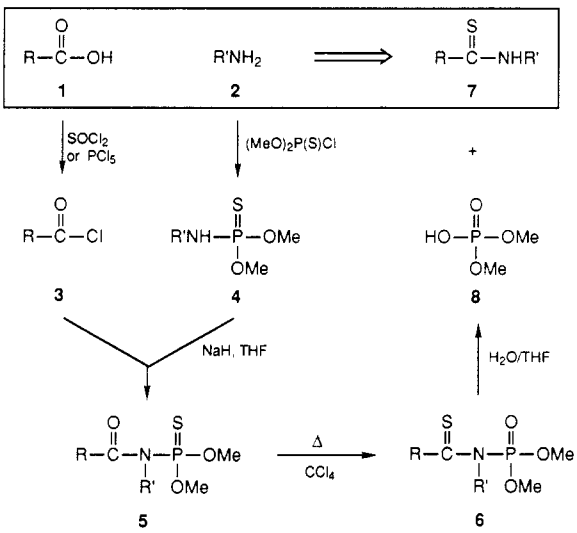
0022-3263/90/1955-6091$02.50/0

Scheme I



will accommodate a variety of other functionalities present (e.g. remote carbonyls) in the carboxylic acid or amine, but is limited to the synthesis of N-monosubstituted thioamides.

Results and Discussion

As indicated in Scheme I, our synthesis of N-substituted thioamides (**7**) from carboxylic acids (**1**) and primary amines (**2**) involves the initial conversion of an amine to a dimethyl phosphoramidothionate (**4**). The sodium salt of **4** is then reacted with the acid chloride (**3**) of a carboxylic acid (**1**) to generate a thiophosphoryl carbonyl mixed imide (**5**). A thermal (ca. 60 °C) rearrangement, which involves an intramolecular transpositioning of the phosphoryl sulfur atom for the carbonyl oxygen atom,[23] forms the corresponding phosphoryl thiocarbonyl mixed imide (**6**). A final hydrolysis cleaves the P–N bond to form dimethylphosphoric acid (**8**) and the desired thioamide (**7**).

We have investigated the conversions of nine different acid chlorides (**3a–i**) derived from carboxylic acids with functionality (R) consisting of simple alkyl (**1a** and **1b**), phenyl (**1c**), bulky alkyl (**1d**), cycloalkylalkyl (**1e**), α,β-unsaturated (**1f**), and remote ketone (**1g**), ester (**1h**), or amide (**1i**) groups. Each of these was reacted with the sodium salt of one or more of the phosphoramidothionates (**4a–c**) derived from methylamine (**2a**), benzylamine (**2b**), or allylamine (**2c**). The thioamides (**7**) synthesized by this method are shown in Figure 1. The structures of the precursors can be readily envisioned by referring to Scheme I. The first letter in the label to each thioamide (**7**) refers to the functionality on carbon (R) while the second letter refers to the substituent on nitrogen (R'). We used the same symbolism for the mixed imide intermediates (**5** and **6**) so that their structures can be easily induced from those shown for the corresponding **7**.

Although the overall conversion of **3** and **4** to **7** (and **8**) is a potential one-pot reaction, we found that a workup following each step avoids a difficult separation at the final step (see below). This also allowed us to identify yields for each step and to further characterize the previously unknown mixed imide intermediates (**5** and **6**).

Preparation of Acid Chlorides (3) and Phosphoramidothionates (4). Acetyl chloride (**3a**), propionyl chloride (**3b**), and benzoyl chloride (**3c**) were obtained commercially. *tert*-Butylacetyl chloride (**3d**), 3-cyclopentylpropionyl chloride (**3e**), 3,3-dimethylacryloyl chloride (**3f**), *cis*-pinonoyl chloride (**3g**), and adipoyl chloride monomethyl ester (**3h**) were prepared from their corresponding acids by standard methods using thionyl chloride or phosphorus pentachloride. It was noticed that *cis*-**3g** epimerized at room temperature over several days to a 75:25 cis:trans mixture, so freshly prepared material was used for the next reaction. *N,N*-Diethyladipamidoyl chloride (**3i**) was prepared by reacting the acid chloride **3h** with diethylamine, hydrolysis of the ester group, and reacting with thionyl chloride in an overall 55% yield.

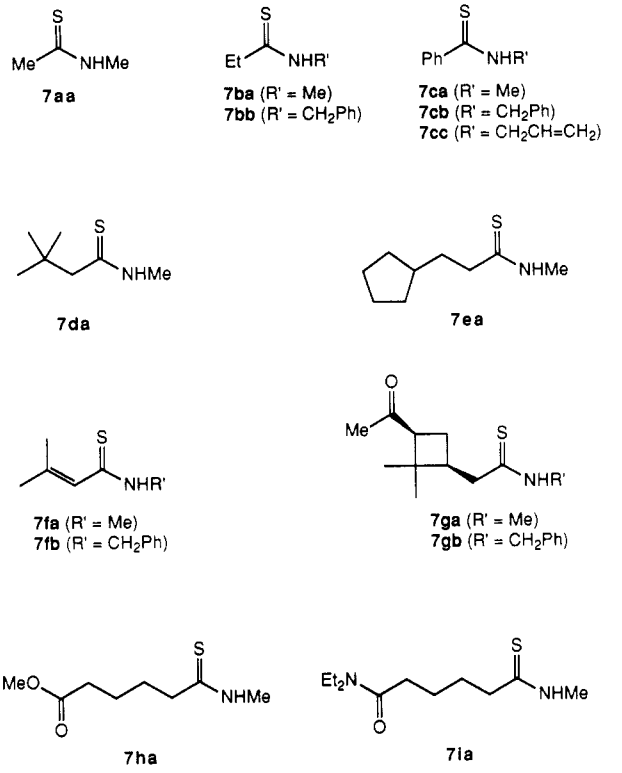


Figure 1. Thioamides synthesized by the method shown in Scheme I.

The reaction of amines with dimethyl chlorothiophosphate (dimethyl phosphorochloridothionate) to form the corresponding phosphoramidothionates (**4**) was straight forward. Excess methyl amine (**1a**) was used to prepare dimethyl *N*-methylphosphoramidothionate (**4a**) while dimethyl *N*-benzylphosphoramidothionate (**4b**) or dimethyl *N*-allylphosphoramidothionate (**4c**) were prepared using 1 equiv of benzylamine (**2b**) or allylamine (**2c**) and triethylamine as a base. Yields after Kugelrohr distillation were 84–87%. Caution: These phosphoramidothionates are potentially toxic.

Conversions of 3 and 4 into Thiophosphoryl Carbonyl Mixed Imides (5). Formation of the sodium salts of the phosphoramidothionates (**4a–c**) with sodium hydride in THF was apparently rapid at room temperature, but the mixtures were warmed to reflux for 2 h to ensure complete reaction. Adding the acid chlorides (**3a–i**) at 0 °C and stirring for 15–30 min completed the conversion.[24] An aqueous workup was employed to remove residual sodium salts but no purification of the products (**5**) was attempted due to their facile rearrangements to **6** (next

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(24) This is a modification of a procedure used to react phosphoramidates with benzoyl chloride. See: Hendrickse, T. F.; Mizrahi, V.; Modro, T. A. *Phosphorus Sulfur* **1984**, *20*, 93.

Table I. Yields and Selected NMR Chemical Shift Data for the Products of the Individual Steps in the Conversion of Acid Chlorides (3) and Phosphoramidothionates (4) of Thioamides (7) via Thiophosphoryl Carbonyl Mixed Imides (5) and Phosphoryl Thiocarbonyl Mixed Imides (6)

reactants		products									
		5			6			7			overall from
3	4	no.	% yield[a]	δ ^{31}P	no.	% yield[b]	δ ^{31}P	no.	% yield[c,d]	δ ^{13}C[e]	3 % yield[d,f]
3a	4a	5aa	80	75.7	6aa	64	4.1	7aa	94	201.3	60
3b	4a	5ba	88	75.9	6ba	63	4.4	7ba	80 (93)	207.5	50 (59)
3b	4b	5bb	86	76.6	6bb	57	4.7	7bb	71 (81)	206.6	40 (46)
3c	4a	5ca	99	74.2	6ca	84	3.4	7ca	80	199.7	67
3c	4b	5cb	99	74.2	6cb	77	3.7	7cb	63 (78)	199.1	49 (60)
3c	4c	5cc	85	74.0	6cc	82	3.4	7cc	45 (95)	199.2	37 (78)
3d	4a	5da	92	75.9	6da	–[g]	4.2	7da	–	203.4	[43 (50)]
3e	4a	5ea	90	75.7	6ea	68	4.2	7ea	84	206.3	57
3f	4a	5fa	82	75.3	6fa	62	4.1	7fa	82	197.4	51
3f	4b	5fb	80	75.9	6fb	51	4.3	7fb	50 (98)	197.1	26 (50)
3g	4a	5ga	83	75.6	6ga	67	4.2	7ga	92	207.9	62
3g	4b	5gb	80	76.3	6gb	59	4.6	7gb	71 (80)	207.7	42 (47)
3h	4a	5ha	75	75.9	6ha	45	4.3	7ha	86 (86)	205.0	39 [50]
3i	4a	5ia	62	75.7	6ia	–[h]	4.1	7ia	–	205.1	– [22]

[a] Percent of 4 converted to 5 by ^{1}H NMR. [b] Isolated yield from 3. [c] Isolated yield from a neutral hydrolysis of purified 6. [d] Isolated yields from an acidic hydrolysis of purified 6 are given in parentheses. [e] Thiocarbonyl carbon. [f] Overall yields without purification of 6 are given in brackets. [g] Decomposes to 7 during chromatography. [h] Not purified.

step). The successful combinations of 3 and 4 attempted are given in Table I. We were not able to form a mixed imide in the reaction of **4a** with pivaloyl chloride (**3**, R = ^{t}Bu). Analysis of each crude product mixture by ^{1}H and ^{31}P NMR revealed the predominant presence of desired mixed imide (**5**) and reactant phosphoramidothionate (**4**). We saw no evidence of Michael addition products in the reactions of **4a** or **4b** anions with **3f** or epimerization in the reactions of **4a** or **4b** anions with **3g**. Also, the ester and amide functionalities in **3h** or **3i** appeared inert to reactions with the anion of **4a**.

The presence of two methoxy groups (6 H) on the phosphorus reagent provides a generally useful probe for a ^{1}H NMR analysis of the product mixture. The POCH_3 doublet (J_{HP} = 14–15 Hz) in **4** is shifted downfield ($\Delta\delta$ = 0.10–0.15 ppm) upon formation of a mixed imide (**5**). Mixed imide formation produces a greater downfield shift in the resonance for the protons on the carbon (R′ group) adjacent to the nitrogen atom. The shift is slightly larger for the *N*-benzyl group ($\Delta\delta$ = ca. 0.8 ppm) than for the *N*-methyl group ($\Delta\delta$ = ca. 0.6 ppm). Interestingly, the protons in the *N*-methyl group become less coupled with phosphorus (ΔJ_{HP} = ca. –2 Hz) while the protons in the *N*-benzyl group become more coupled (ΔJ_{HP} = ca. +3 Hz). ^{31}P NMR resonances of **4** and **5** were similar in general but more distinct for the *N*-benzoyl (R = Ph) analogues.

The yields for **5** given in Table I are not isolated yields but reflect the ratio of **4** to **5** in the crude product mixture as determined by ^{1}H NMR spectroscopy. Finding recovered phosphoramidothionate (**4**) in the product mixture may indicate incomplete formation of its sodium salt; however, we feel this is unlikely since the conversions of **4a** and **4b** into **5ca** and **5cb** with benzoyl chloride (**3c**) are reproducibly complete. More likely, **4** is *re-formed* from the sodium salt of **4** by a competing E_2 elimination of HCl from the acid chlorides (**3**) to form ketene side products. Acetyl chloride (**3a**) and 3,3-dimethylacryloyl chloride (**3f**) are sterically unhindered for ketene formation and do give slightly lower yields of mixed imide.[25] Steric bulk in the phosphoramidothionate anion appears to promote more ketene formation. In a preliminary investigation, we found that reacting acetyl chloride (**3a**) with the sodium salt of dimethyl *N*-isopropylphosphoramidothionate (**4**, R′ = isopropyl) gave considerably less (14%) mixed imide (**5**, R = Me; R′ = isopropyl) and more (86%) re-formed phosphoramidothionate. Proton abstraction from the carbon adjacent to the remote carbonyl groups in pinonoyl chloride (**3g**) and the adipoyl chlorides (**3h** and **3i**) could also cause re-formation of **4** but the expected Dieckmann type condensation products were not detected.

Rearrangement of Thiophosphoryl Carbonyl Mixed Imides (5) to Phosphoryl Thiocarbonyl Mixed Imides (6). We recently discovered[23] that certain thiophosphoryl carbonyl mixed imides (**5**) undergo an uncatalyzed thermal (20–60 °C) intramolecular rearrangement in inert solvents to form thiocarbonyl phosphoryl mixed imides (**6**). A substituent on nitrogen (**5**, R′ ≠ H) was found to be necessary for the rearrangement and limits our application of the rearrangement to the synthesis of N-monosubstituted thioamides.

Although rearrangement occurs at similar rates in solvents of varying polarity,[26] we chose to perform the rearrangements, for this study, in carbon tetrachloride at reflux. At the boiling point of carbon tetrachloride, the *N*-benzoyl mixed imides (**5ca–5cc**) and the *N*-(3,3-dimethylacryloyl) mixed imides (**5fa** and **5fb**) were completely rearranged in 1 h while most of the aliphatic mixed imides required ca. 6 h. Surprisingly, the bulky *tert*-butylacetyl mixed imide (**5da**) required only 35 min and only rearranged to an apparent 25:75 equilibrium mixture of **5da**:**6da**.

We have noticed that prolonged heating of the rearranged mixed imides (**6**) in carbon tetrachloride results in some decomposition by an intermolecular process. Therefore, the desired unimolecular rearrangement of **5** to **6** was carried out at relatively low concentrations (0.1 M) and carefully monitored. Visually, the rearrangement is very noticeable due to the development of a deep yellow or orange color. On TLC (silica gel, dichloromethane), **6** has a smaller R_f than **5**. In the ^{1}H NMR, rearrangement produces a downfield shift ($\Delta\delta$ = ca. 0.4 ppm) of the protons on carbon adjacent to the nitrogen (R′ group) and a decrease in their coupling with phosphorus (ΔJ_{HP} = ca.

(25) Other workers[25a] were unable to obtain any phosphoryl carbonyl mixed imide product upon reacting the sodium salt of dimethyl *N*-methylphosphoramidate with acetyl chloride. They also attributed this to a proton abstraction with ketene formation. Apparently, a phosphoramidothioate anion is more nucleophilic than the corresponding phosphoramidate anion even though they may have similar basicities.[25b] See: (a) Mizrahi, V.; Modro, T. A. *J. Org. Chem.* **1982**, *47*, 3533. (b) Williams, A.; Douglas, K. T.; Loran, J. S. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1010.

(26) DeBruin, K. E.; Boros, E. E., unpublished results.

-3 Hz for both the *N*-methyl and *N*-benzyl groups). A characteristic decrease in the coupling constant between the $POCH_3$ protons and phosphorus is also observed (ΔJ_{HP} = -2-3 Hz). ^{31}P NMR gives unambiguous evidence that the thiophosphoryl has been converted to a phosphoryl (Table I).[27]

Workup of the reaction involved a simple evaporation of the solvent and purification by flash column chromatography (silica gel, eluting with 5-20% ethyl acetate in dichloromethane). Isolated yields for the overall conversions of acid chlorides (**3**) to rearranged mixed imides (**6**), via **5**, are given in Table I. We found that the procedure involving an aqueous workup immediately after forming **5** from **3**, followed by the rearrangement of **5** to **6** in carbon tetrachloride, gave better overall yields than a direct one-pot conversion of **3** to **6** in the crude THF reaction mixture at reflux. The chromatographic purification undoubtedly results in some loss of rearranged mixed imide (**6**) since in one case (**6da**), complete cleavage of the rearranged mixed imide (to form thioamide **7da**) occurred on the column. In spite of this, we found it desirable in most cases to purify **6** at this stage due to difficulties in chromatographically separating residual phosphoramidothionates (**4**) from thioamides (**7**) formed after hydrolysis (next step). The bright colors of the rearranged mixed imides (**6**) also made chromatography at this point particularly convenient from the standpoint of on-column visualization.

Hydrolysis of Phosphoryl Thiocarbonyl Mixed Imides (6) to Thioamides (7). The hydrolysis of the rearranged mixed imides (**6**) was carried out in a 2:1 THF-water solution. The reactions were monitored by TLC (silica gel, dichloromethane) and required from 1-3 days at room temperature. Extracting the reaction mixtures with dichloromethane left the dimethylphosphoric acid (**8**) in the aqueous layer and provided the crude products. If the rearranged mixed imides (**6**) were purified before hydrolysis, purification of the desired thioamide products (**7**) required only a rapid vacuum liquid chromatography (silica gel, 0-75% ethyl acetate in dichloromethane). Isolated yields of **7** from this hydrolysis step are given in Table I along with the very characteristic ^{13}C NMR chemical shifts of the thiocarbonyl carbon.[28]

The hydrolysis proceeded by P-N bond cleavage, but in many cases, a significant amount of carboxamide (**9**, RC(O)NHR') was produced along with the desired thioamide (**7**). We had no difficulty in isolating pure thioamide since the slower eluting carboxamide (**9**) is easily removed from the thioamide (**7**) by chromatography. The isolated yields for **7**, given in Table I, largely reflect the amount of carboxamide side product and not a further hydrolysis of **7** or **9** to a carboxylic acid. Control experiments (see the Experimental Section) established that the carboxamide (**9**) does not derive from the thioamide (**7**) under the reaction conditions[29] but is a true side product produced during the cleavage.[30]

Because of the formation of carboxamide side products (**9**) and the relatively long reaction times needed, we investigated the effect of adding acid to the aqueous medium for hydrolysis of some of the rearranged mixed imides (**6**). The presence of hydrochloric acid (0.3-0.5 M HCl in aqueous THF) significantly increased the rate of hyrolysis (5-10-fold) and in general gave higher yields due to the production of less amide side product. For **7cc** and **7fb**, in particular, the increase in yield was dramatic. These acid hydrolysis yields for the conversions investigated are given in parentheses in Table I.

As mentioned above, a chromatographic purification of the rearranged mixed imide (**6**), to remove residual **4** before hydrolysis, was performed but likely results in some on-column cleavage. This purification decreases the yield of isolated **6** but does produce the desired thioamide (**7**). We found that with the more polar thioamides (**7ha** and **7ia**) it was possible to avoid the purification and separate **4** from the thioamides by chromatography after hydrolysis. These yields are indicated by brackets in the last column of Table I.

Summary

Utilizing the conversions shown in Scheme I, we have been able to prepare a variety of N-substituted thioamides (**7**, Figure 1). The procedure has a number of attractive features:

1. The reagent, dimethyl chlorothiophosphate, used to derivatize the primary amines is inexpensive and the resulting phosphoramidothionates (**4**) needed to accomplish the overall thioamidations, are relatively odorless.

2. Each step in the overall conversion can be carried out under relatively mild conditions. Formation of the mixed imides (**5**) is rapid at 0 °C. The rearrangements of **5** to **6** may be accomplished at room temperatures if desired. Hydrolysis of the rearranged mixed imides (**6**) occurs at room temperature in aqueous THF but is greatly accelerated by the presence of dilute hydrochloric acid.

3. The overall conversion is compatable with the presence of a variety of other functionalities in the acid chloride.[31] Formation of **5** occurs without promoting base-catalyzed condensation reactions or epimerizations at a chiral center adjacent to a ketone functionality. Most importantly, remote carbonyl groups (ketones, esters, and amides) do not undergo thionation.

4. The methodology is likely to be compatable with a variety of substituents on nitrogen but steric bulk in the immediate vicinity of the amine nitrogen (e.g. *N*-isopropyl) results in a lower yield for mixed imide (**5**) formation.

5. The yields for the overall conversion (50-80% in general) are very good considering a three-step process with workups at each stage and two purifications. An acidic hydrolysis of the rearranged mixed imides (**6**) significantly improves the yields by reducing the formation of carboxamides (**9**).

6. Isolating pure thioamides (**7**) is simplified by the fact that dimethylphosphoric acid (**8**) produced during the hydrolysis remains in the aqueous layer upon workup.

7. Finally, and potentially significant, the procedure involves the intermediacy of the mixed imide (**6**), an N-phosphorylated N-monosubstituted thioamide. Thus, before cleavage, the phosphoryl group can act as a temporary N-H protecting group and allow for direct enolate anion elaboration at the α-position of the thiocarbonyl if so desired.

(27) *Phosphorus-31 NMR: Principles and Applications*; Gorenstein, D. G., Ed.; Academic Press: Orlando, FL, 1984.

(28) Scheibye, S.; Pedersen, B. S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229.

(29) Acidic hydrolysis of thioamides usually leads to a carboxylic acid and only rarely results in the formation of an amide product.[1]

(30) A possible route for the formation of carboxamide (**9**) from **6** involves a tautomerism of phosphorus from nitrogen to sulfur and subsequent hydrolysis with C-S bond cleavage. See: (a) Mikolajczyk, M.; Kielbasinski, P.; Goszczynska, Z. *J. Org. Chem.* **1977**, *42*, 3629. (b) Zimin, M. G.; Zabirov, N. G.; Kamalov, R. M.; Pudovik, A. N. *Zh. Obshch. Khim.* **1986**, *56*, 2660. (c) Mikolajczyk, M.; Kielbasinski, P.; Sut, A. *Tetrahedron* **1986**, *42*, 4591. (d) Baraniak, J.; Stec, W. J. *Phosphorus Sulfur* **1986**, *29*, 115.

(31) Any source of acid chlorides can be utilized. For examples, see: Ansell, M. F. In *The Chemistry of Acyl Halides*; Patai, S., Ed.; Interscience: New York, 1972, pp 35-68.

Experimental Section

General. All boiling points refer to Kugelrohr oven temperatures. Melting points are uncorrected. All NMR spectra were measured in $CDCl_3$ solutions. ^1H NMR spectra were recorded at 60, 270, or 300 MHz. Multiplicity is denoted by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), and br (broad). Coupling constants (J, hertz) refer to hydrogen–hydrogen coupling unless noted otherwise. ^{13}C NMR spectra were recorded at 67.9 or 75.5 MHz. ^{31}P NMR spectra were recorded at 121.5 MHz. Infrared (IR) spectra were measured as thin films on NaCl plates unless otherwise stated. The data obtained for known compounds compared well with that found in the literature and the references are given without details.

Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone, CH_2Cl_2 was distilled from calcium hydride, and water was deionized and distilled. Carbon tetrachloride was spectral grade and used without purification. Chromatographic separations were accomplished using Merck silica gel (grade 60, 230–400 mesh). Dimethyl phosphorochloridothionate (dimethyl chlorothiophosphate) and the amines (**2a–c**) used to prepare dimethyl N-substituted phosphoramidothionates (**4a–c**) as described below were obtained commercially. Acetyl chloride (**3a**), propionyl chloride (**3b**), and benzoyl chloride (**3c**) were obtained commercially and purified by distillation. *tert*-Butylacetyl chloride (**3d**), 3-cyclopentylpropionyl chloride (**3e**), and 3,3-dimethylacryloyl chloride (**3f**) are commercially available but were prepared from the corresponding acids by standard methods. Carboxylic acid chlorides (**3g** and **3h**) were prepared as described below from commercially available carboxylic acids (**1g** and **1h**). Carboxylic acid (**1i**) was prepared from acid chloride (**3h**) and converted to acid chloride (**3i**) as described below.

***cis*-(3-Acetyl-2,2-dimethylcyclobutyl)ethanoyl Chloride (3g) from *cis*-Pinonic Acid (1g).** A stirring solution of **1g** (1.00 g, 5.43 mmol) in ether (40 mL) was cooled to 0 °C, and pyridine (0.43 g, 5.43 mmol) was added in one portion followed by the slow, dropwise addition of thionyl chloride (0.77 g, 6.47 mmol). After 15 min at 0 °C, the white reaction mixture was allowed to warm to room temperature and vacuum filtered through a glass frit. Concentrating in vacuo at 25–30 °C gave pure **3g** (1.08 g, 5.33 mmol, 98% yield) as a colorless oil; bp 95 °C (0.25 mm); IR ν 2957, 2926, 1806, 1701, 1465, 1371, 1357, 1227, 1183, 1037, 966, 720, 691, 601 cm^{-1}; ^1H NMR δ 2.91 (1 H, dd, J = 7, 14), 2.90 (2 H, d, J = 8), 2.46 (1 H, m), 1.99 (2 H, m), 2.06 (3 H, s), 1.36 (3 H, s), 0.88 (3 H, s). (lit.[32] IR, ^1H NMR.)

6-Methoxy-6-oxohexanoyl Chloride (3h) from Adipic Acid Monomethyl Ester (1h). A solution of **1h** (0.75 g, 4.68 mmol) in ether (3 mL) was added dropwise to a stirred mixture of phosphorus pentachloride (1.02 g, 4.90 mmol) in ether (5 mL) at room temperature. Evolution of hydrogen chloride was observed along with the gradual disappearance of the solid reagent. Following the addition, the reaction mixture was stirred an additional 2 min, filtered, and concentrated in vacuo to provide pure **3h** (0.84 g, 4.68 mmol, 100% yield) as a colorless oil: bp 58 °C (0.10 mm); IR ν 2954, 2874, 1801, 1737, 1437, 1367, 1201, 1176 cm^{-1}; ^1H NMR δ 3.68 (3 H, s), 2.93 (2 H, t, J = 7), 2.35 (2 H, t, J = 7), 1.72 (4 H, m).

6-(Diethylamino)-6-oxohexanoic Acid (1i) from 3h. A solution of diethylamine (1.03 g, 14.1 mmol) and triethylamine (1.43 g, 14.1 mmol) in ether (30 mL) was added dropwise to a stirred solution of **3h** (2.52 g, 14.1 mmol) in ether (30 mL) at room temperature. The white reaction mixture was stirred for 30 min and then vacuum filtered through a glass frit. The filtrate was concentrated in vacuo, and the resulting oil was purified by Kugelrohr distillation to provide methyl 6-(diethylamino)-6-oxohexanoate (**1i** methyl ester, 2.91 g, 13.5 mmol, 96% yield) as a colorless liquid: bp 100 °C (0.09 mm); IR ν 2971, 1739, 1641, 1434 cm^{-1}; ^1H NMR δ 3.67 (3 H, s), 3.38 (2 H, q, J = 7.1), 3.32 (2 H, q, J = 7.1), 2.35 (4 H, m), 1.68 (4 H, m), 1.18 (3 H, t, J = 7.1), 1.11 (3 H, t, J = 7.1). All of this material was dissolved in a mixture of 5% aqueous KOH (50 mL) and methanol (20 mL), and the solution was stirred at room temperature for 30 min. After removing the methanol in vacuo, the aqueous mixture was extracted with ether (3 × 20 mL) and then acidified with concentrated HCl. The acidic aqueous layer was extracted again with ether (3 × 20 mL), and the latter organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo to provide **1i** (2.23 g, 11.1 mmol, 80% yield) as a colorless, viscous oil: IR ν 3500–2500 (broad OH stretch), 2974, 1713, 1603, 1462, 1219, 912, 729 cm^{-1}; ^1H NMR δ 10.29 (1 H, br s), 3.38 (2 H, q, J = 7.1), 3.32 (2 H, q, J = 7.1), 2.37 (4 H, m), 1.69 (4 H, m), 1.18 (3 H, t, J = 7.1), 1.11 (3 H, t, J = 7.1). Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.51. Found: C, 59.45; H, 9.37.

6-(Diethylamino)-6-oxohexanoyl Chloride (3i) from 1i. By using thionyl chloride as described above for **3g**, **3i** was prepared as a colorless liquid: 72% yield after Kugelrohr distillation; bp 105 °C (0.04 mm); IR ν 2973, 2934, 2875, 1799, 1642, 1431 cm^{-1}; ^1H NMR δ 3.40 (4 H, q, J = 7), 2.97 (2 H, br t, J = 6), 2.49 (2 H, br t, J = 6), 1.78 (4 H, m), 1.19 (6 H, t, J = 7).

Dimethyl *N*-Methylphosphoramidothionate (4a) from Methylamine (2a). Excess **2a** (9.46 g, 304.6 mmol) was added dropwise to a stirred solution of dimethyl phosphorochloridothionate (20.38 g, 126.9 mmol) in ether (230 mL) by way of a dry ice condenser. Following this addition, the white reaction mixture was stirred an additional 30 min, vacuum filtered through a glass frit, and concentrated in vacuo. A Kugelrohr distillation provided **4a** (17.18 g, 110.7 mmol, 87% yield) as a colorless liquid: bp 55 °C (0.3 mm); IR ν 3331, 2946, 2842, 1458, 1385, 1181, 1099, 1027, 861, 811, 631 cm^{-1}; ^1H NMR δ 3.68 (6 H, d, J_{HP} = 14), 3.20 (1 H, br s), 2.63 (3 H, dd, J = 5, J_{HP} = 12); ^{31}P NMR δ 77.4. Anal. Calcd for $C_3H_{10}NO_2PS$: C, 23.22; H, 6.50. Found: C, 23.11; H, 6.63. (lit.[33] bp, IR.)

Dimethyl *N*-Benzylphosphoramidothionate (4b) from Benzylamine (2b). A solution of **2b** (1.07 g, 10.0 mmol) and triethylamine (1.01 g, 10.0 mmol) in dichloromethane (20 mL) was added dropwise to a stirred solution of dimethyl phosphorochloridothionate (1.6 g, 10.0 mmol) in dichloromethane (20 mL). After stirring at room temperature for an additional 20 h, the reaction mixture was washed with 1 M HCl (2 × 15 mL) and water (1 × 15 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. A Kugelrohr distillation gave **4b** (1.94 g, 8.39 mmol, 84% yield) as a light yellow oil: bp 122 °C (0.11 mm); IR ν 3297, 3028, 2945, 2842, 1496, 1454, 1406, 1206, 1181, 1024, 909, 860, 816, 736, 699, 638 cm^{-1}; ^1H NMR δ 7.27 (5 H, s), 4.15 (2 H, dd, J = 7, J_{HP} = 11), 3.66 (6 H, d, J_{HP} = 14), 3.60 (1 H, br s); ^{31}P NMR δ 76.1. Anal. Calcd for $C_9H_{14}NO_2PS$: C, 46.75; H, 6.10. Found: C, 46.69; H, 5.99.

Dimethyl *N*-Allylphosphoramidothionate (4c) from Allylamine (2c). By the procedure used to prepare **4b**, **4c** was obtained as a colorless liquid: 87% yield after Kugelrohr distillation; bp 65 °C (0.05 mm); IR ν 3312, 3081, 2984, 2946, 2843, 1645, 1441, 1406, 1238, 1181, 1134, 1032, 924, 812, 646 cm^{-1}; ^1H NMR δ 5.86 (1 H, ddt, J = 17.1, 10.2, 5.4), 5.23 (1 H, ddt, J = 17.1, 1.4, 1.5), 5.13 (1 H, ddt, J = 10.2, 1.4, 1.3), 3.70 (6 H, d, J_{HP} = 13.7), 3.57 (2 H, ddd, J_{HP} = 11.1, J = 5.4, 5.4), 3.15 (1 H, br s); ^{31}P NMR δ 76.1. Anal. Calcd for $C_5H_{12}NO_2PS$: C, 33.14; H, 6.68. Found: C, 33.41; H, 6.49. (lit.[34] bp, IR, ^1H NMR, ^{31}P NMR.)

General Procedure for the Synthesis of Thiophosphoryl Carbonyl Mixed Imides (5) from Acid Chlorides (3) and Phosphoramidothionates (4). In a typical experiment, a solution of **4** (3.00 mmol) in THF (4 mL) was added dropwise to a stirred suspension of sodium hydride (3.75 mmol) in THF (2 mL) at room temperature under a nitrogen atmosphere. After the evolution of hydrogen gas subsided, the mixture was warmed to reflux and maintained for approximately 2 h. The reaction mixture was then cooled to 0 °C, and **3** (3.00 mmol) in THF (4 mL) was added dropwise. The resulting mixture was then stirred for 15–30 min while warming to room temperature. Workup was performed in the reaction vessel as follows: dichloromethane (8 mL) was added to the flask, and the mixture was quenched with water (8 mL). After inverting several times, the lower organic layer was removed by pipet. The aqueous layer was extracted three times with dichloromethane (3 × 5 mL), and the combined organic layers were dried over $MgSO_4$ and vacuum filtered through a glass frit

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containing a small plug of Celite. The filtrate was concentrated in vacuo to afford a crude product mixture consisting of desired product (**5**), recovered starting phosphoramidothionate (**4**), and, in some cases, traces of rearranged product (**6**). The percent of **5** in the product mixture was determined by ^{1}H NMR and is given in Table I. Specific spectral data on each thiophosphoryl carbonyl mixed imide (**5**) synthesized is given below. The product mixture was used for the next step without further purification.

Dimethyl *N*-ethanoyl-*N*-methylphosphoramidothionate (5aa) from 3a and 4a: light yellow oil; IR ν 2980, 2944, 2835, 1680, 1360, 1246, 1010, 910, 800, 686, 608 cm^{-1}; ^{1}H NMR δ 3.83 (6 H, d, J_{HP} = 15), 3.20 (3 H, d, J_{HP} = 10), 2.40 (3 H, s); ^{31}P NMR δ 75.7.

Dimethyl *N*-propanoyl-*N*-methylphosphoramidothionate (5ba) from 3b and 4a: light yellow oil; IR ν 2980, 2948, 1693, 1460, 1418, 1361, 1198, 1021, 912, 815, 731, 643 cm^{-1}; ^{1}H NMR δ 3.80 (6 H, d, J_{HP} = 14), 3.18 (3 H, d, J_{HP} = 10), 2.66 (2 H, q, J = 7), 1.14 (3 H, t, J = 7); ^{31}P NMR δ 75.9.

Dimethyl *N*-propanoyl-*N*-benzylphosphoramidothionate (5bb) from 3b and 4b: light yellow oil; IR ν 3031, 2948, 2845, 1690, 1454, 1208, 1182, 1031, 911, 817, 731, 647 cm^{-1}; ^{1}H NMR δ 7.29 (5 H, s), 4.99 (2 H, d, J_{HP} = 14), 3.75 (6 H, d, J_{HP} = 15), 2.72 (2 H, q, J = 7), 1.21 (3 H, t, J = 7); ^{31}P NMR δ 76.6.

Dimethyl *N*-benzoyl-*N*-methylphosphoramidothionate (5ca) from 3c and 4a: yellow oil; IR ν 3050, 2940, 2830, 1665, 1440, 1285, 1024, 800, 735, 650 cm^{-1}; ^{1}H NMR δ 7.65–7.30 (5 H, m), 3.63 (6 H, d, J_{HP} = 14), 3.13 (3 H, d, J_{HP} = 9); ^{31}P NMR δ 74.2.

Dimethyl *N*-benzoyl-*N*-benzylphosphoramidothionate (5cb) from 3c and 4b: orange oil; IR ν 3029, 2943, 2849, 1674, 1443, 1274, 1038, 816, 729, 700, 643 cm^{-1}; ^{1}H NMR δ 7.10–7.67 (10 H, m), 4.96 (2 H, d, J_{HP} = 12), 3.57 (6 H, d, J_{HP} = 15); ^{31}P NMR δ 74.2.

Dimethyl *N*-benzoyl-*N*-allylphosphoramidothionate (5cc) from 3c and 4c: orange oil; IR ν 3063, 2986, 2950, 2846, 1673, 1601 cm^{-1}; ^{1}H NMR δ 7.73–7.20 (5 H, m), 5.90 (1 H, m), 5.43–5.00 (2 H, m), 4.38 (2 H, dd, J = 5, J_{HP} = 13), 3.66 (6 H, d, J_{HP} = 14); ^{31}P NMR δ 74.0.

Dimethyl *N*-(3,3-dimethylbutanoyl)-*N*-methylphosphoramidothionate (5da) from 3d and 4a: light yellow oil; IR ν 2870, 2845, 2830, 1695, 1460, 1360, 1225, 1170, 1015, 930, 805, 645 cm^{-1}; ^{1}H NMR δ 3.80 (6 H, d, J_{HP} = 15), 3.16 (3 H, d, J_{HP} = 10), 2.59 (2 H, s), 1.14 (9 H, s); ^{31}P NMR δ 75.9.

Dimethyl *N*-(3-cyclopentylpropanoyl)-*N*-methylphosphoramidothionate (5ea) from 3e and 4a: light yellow oil; IR ν 2949, 2866, 1691, 1453, 1192, 1024, 933, 812, 652 cm^{-1}; ^{1}H NMR δ 3.82 (6 H, d, J_{HP} = 15), 3.18 (3 H, d, J_{HP} = 10), 2.70 (2 H, t, J = 7), 1.67–1.00 (11 H, m); ^{31}P NMR δ 75.7.

Dimethyl *N*-(3-methylbut-2-enoyl)-*N*-methylphosphoramidothionate (5fa) from 3f and 4a: orange oil; IR ν 2870, 2819, 1675, 1635, 1443, 1223, 1165, 1020, 930, 810, 639 cm^{-1}; ^{1}H NMR δ 6.18 (1 H, br s), 3.78 (6 H, d, J_{HP} = 15), 3.17 (3 H, d, J_{HP} = 10), 2.12 (3 H, d, J = 1), 1.95 (3 H, d, J = 1); ^{31}P NMR δ 75.3.

Dimethyl *N*-(3-methylbut-2-enoyl)-*N*-benzylphosphoramidothionate (5fb) from 3f and 4b: orange oil; IR ν 2947, 2845, 1674, 1635, 1226, 1168, 1028, 824, 652 cm^{-1}; ^{1}H NMR δ 7.50–7.17 (5 H, m), 6.28 (1 H, br s), 5.04 (2 H, d, J_{HP} = 14), 3.73 (6 H, d, J_{HP} = 15), 2.13 (3 H, d, J = 1), 1.95 (3 H, d, J = 1); ^{31}P NMR δ 75.9.

Dimethyl *N*-((*cis*-3-acetyl-2,2-dimethylcyclobutyl)ethanoyl)-*N*-methylphosphoramidothionate (5ga) from 3g and 4a: light yellow oil; IR ν 2873, 2830, 1700, 1455, 1378, 1360, 1170, 1020, 920, 805, 635 cm^{-1}; ^{1}H NMR δ 3.81 (6 H, d, J_{HP} = 14), 3.14 (3 H, d, J_{HP} = 10), 2.86 (1 H, m), 2.66 (2 H, m), 2.50 (1 H, m), 2.08 (3 H, s), 1.99 (2 H, m), 1.43 (3 H, s), 0.92 (3 H, s); ^{31}P NMR δ 75.6.

Dimethyl *N*-((*cis*-3-acetyl-2,2-dimethylcyclobutyl)ethanoyl)-*N*-benzylphosphoramidothionate (5gb) from 3g and 4b: light yellow oil; IR ν 3062, 3030, 2950, 2871, 1702, 1605, 1179, 1028, 816 cm^{-1}; ^{1}H NMR δ 7.37–7.20 (5 H, m), 4.97 (2 H, d, J_{HP} = 14.2), 3.73 (3 H, d, J_{HP} = 14.4), 3.72 (3 H, d, J_{HP} = 14.3), 2.87 (1 H, dd, J = 7.7, 9.9), 2.68 (1 H, d, J = 8), 2.65 (1 H, d, J = 7), 2.47 (1 H, m), 2.01 (3 H, s), 1.88 (2 H, m), 1.29 (3 H, s), 0.76 (3 H, s); ^{31}P NMR δ 76.3.

Dimethyl *N*-(6-methoxy-6-oxohexanoyl)-*N*-methylphosphoramidothionate (5ha) from 3h and 4a: light yellow oil; IR ν 2951, 2852, 1736, 1685, 1437, 1367, 1283, 1181, 1028, 790 cm^{-1}; ^{1}H NMR δ 3.80 (6 H, d, J_{HP} = 14), 3.73 (3 H, s), 3.17 (3 H, d, J_{HP} = 10), 2.67 (2 H, m), 2.34 (2 H, m), 1.68 (4 H, m); ^{31}P NMR δ 75.9.

Dimethyl *N*-(6-(diethylamino)-6-oxohexanoyl)-*N*-methylphosphoramidothionate (5ia) from 3i and 4a: light yellow oil; IR ν 2947, 2874, 1690, 1639, 1460, 1029, 812, 649 cm^{-1}; ^{1}H NMR δ 3.79 (6 H, d, J_{HP} = 14.3), 3.37 (2 H, q, J = 7.1), 3.31 (2 H, q, J = 7.1), 3.17 (3 H, d, J_{HP} = 10.0), 2.68 (2 H, m), 2.33 (2 H, m), 1.69 (4 H, m), 1.17 (3 H, t, J = 7.1), 1.11 (3 H, t, J = 7.1); ^{31}P NMR δ 75.7.

General Procedure for the Conversion of Thiophosphoryl Carbonyl Mixed Imides (5) to Phosphoryl Thiocarbonyl Mixed Imides (6). In a typical experiment, a solution of the crude **5**, obtained above, in carbon tetrachloride (ca. 0.1 M) was heated to reflux and maintained while monitoring the progress of the rearrangement by TLC (silica gel, CH_2Cl_2, **6** has a lower R_f than **5**) and ^{1}H NMR. When the reaction was complete, the solution was concentrated in vacuo to provide the crude product. Product **6ia** was not purified but carried directly on to the next step. All other products were purified by flash chromatography on silica gel, eluting with 5–20% ethyl acetate/CH_2Cl_2. Isolated yields are given in Table I. Product **6da** was unstable to the chromatography on silica gel and underwent cleavage of the phosphoryl group to form **7da**.

Dimethyl *N*-thioethanoyl-*N*-methylphosphoramidate (6aa): yellow oil; 64% yield from **3a**; IR ν 2954, 2852, 1461, 1369, 1300, 1184, 1022, 966, 846 cm^{-1}; ^{1}H NMR δ 3.87 (6 H, d, J_{HP} = 12), 3.53 (3 H, d, J_{HP} = 7), 2.97 (3 H, s); ^{31}P NMR δ 4.1. Anal. Calcd for $C_5H_{12}NO_3PS$: C, 30.46; H, 6.13. Found: C, 30.19; H, 5.94.

Dimethyl *N*-thiopropanoyl-*N*-methylphosphoramidate (6ba): yellow oil; 63% yield from **3b**; IR ν 2955, 2852, 1460, 1281, 1029, 847 cm^{-1}; ^{1}H NMR δ 3.84 (6 H, d, J_{HP} = 12), 3.51 (3 H, d, J_{HP} = 7), 3.15 (2 H, q, J = 7), 1.34 (3 H, t, J = 7); ^{31}P NMR δ 4.4. Anal. Calcd for $C_6H_{14}NO_3PS$: C, 34.12; H, 6.68. Found: C, 33.84; H, 6.61.

Dimethyl *N*-thiopropanoyl-*N*-benzylphosphoramidate (6bb): yellow oil; 57% yield from **3b**; IR ν 3030, 2955, 2852, 1453, 1372, 1330, 1279, 1192, 1028, 969, 833 cm^{-1}; ^{1}H NMR δ 7.35–7.20 (5 H, m), 5.54 (2 H, d, J_{HP} = 11), 3.68 (6 H, d, J_{HP} = 12), 3.13 (2 H, q, J = 7), 1.35 (3 H, t, J = 7); ^{31}P NMR δ 4.7. Anal. Calcd for $C_{12}H_{18}NO_3PS$: C, 50.17; H, 6.31. Found: C, 50.37; H, 6.38.

Dimethyl *N*-thiobenzoyl-*N*-methylphosphoramidate (6ca): orange oil; 84% yield from **3c**; IR ν 3050, 3010, 2944, 2843, 1438, 1280, 1030, 950, 820, 745, 683 cm^{-1}; ^{1}H NMR δ 7.50–7.35 (5 H, m), 3.59 (6 H, d, J_{HP} = 12), 3.54 (3 H, d, J_{HP} = 7); ^{31}P NMR δ 3.4. Anal. Calcd for $C_{10}H_{14}NO_3PS$: C, 46.33; H, 5.44. Found: C, 46.30; H, 5.55.

Dimethyl *N*-thiobenzoyl-*N*-benzylphosphoramidate (6cb): orange oil; 77% yield from **3c**; IR ν 3061, 3030, 2954, 2852, 1445, 1294, 1194, 1054, 948, 830, 766, 700 cm^{-1}; ^{1}H NMR δ 7.60–7.13 (10 H, m), 5.50 (2 H, d, J_{HP} = 9), 3.53 (6 H, d, J_{HP} = 12); ^{31}P NMR δ 3.7. Anal. Calcd for $C_{16}H_{18}NO_3PS$: C, 57.30; H, 5.41. Found: C, 57.11; H, 5.50.

Dimethyl *N*-thiobenzoyl-*N*-allylphosphoramidate (6cc): orange oil; 82% yield from **3c**; IR ν 3058, 2955, 2853, 1488, 1444, 1294, 1210, 1036, 829, 762, 697 cm^{-1}; ^{1}H NMR δ 7.43–7.27 (5 H, m), 5.98 (1 H, ddt, J = 17, 10, 6), 5.34 (1 H, ddt, J = 1.4, 17, 1.4), 5.26 (1 H, ddt, J = 1.4, 10, 1.4), 4.86 (2 H, ddt, J_{HP} = 10, J = 6, 1.4), 3.61 (6 H, d, J_{HP} = 11.4); ^{31}P NMR δ 3.4. Anal. Calcd for $C_{12}H_{16}NO_3PS$: C, 50.52; H, 5.65. Found: C, 50.42; H, 5.62.

Dimethyl *N*-(3,3-dimethylthiobutanoyl)-*N*-methylphosphoramidate (6da): ^{1}H NMR δ 3.83 (6 H, d, J_{HP} = 12), 3.45 (2 H, s), 3.42 (3 H, d, J_{HP} = 7), 1.13 (9 H, s); ^{31}P NMR δ 4.2.

Dimethyl *N*-(3-cyclopentylthiopropanoyl)-*N*-methylphosphoramidate (6ea): yellow oil; 68% yield from **3e**; IR ν 2948, 2863, 1459, 1282, 1184, 1024, 845, 774 cm^{-1}; ^{1}H NMR δ 3.84 (6 H, d, J_{HP} = 12), 3.52 (3 H, d, J_{HP} = 7), 3.40–3.07 (2 H, m), 2.10–1.00 (11 H, m); ^{31}P NMR δ 4.2. Anal. Calcd for $C_{11}H_{22}NO_3PS$: C, 47.30; H, 7.94. Found: C, 47.48; H, 8.09.

Dimethyl *N*-(3-methylthiobut-2-enoyl)-*N*-methylphosphoramidate (6fa): orange oil; 62% yield from **3f**; IR ν 2954, 2911, 2852, 1640, 1446, 1257, 1186, 1046, 866, 816 cm^{-1}; ^{1}H NMR δ 6.33 (1 H, br s), 3.81 (6 H, d, J_{HP} = 12), 3.52 (3 H, d, J_{HP} = 7), 1.97 (3 H, d, J = 1), 1.93 (3 H, d, J = 1); ^{31}P NMR δ 4.1. Anal.

Calcd for $C_8H_{16}NO_3PS$: C, 40.50; H, 6.80. Found: C, 40.67; H, 6.68.

Dimethyl *N*-(3-methylthiobut-2-enoyl)-*N*-benzylphosphoramidate (6fb): orange oil; 51% yield from **3f**; IR ν 3063, 3030, 2955, 2911, 2852, 1642, 1496, 1454, 1322, 1280, 1218, 1172, 1032, 851, 821 cm^{-1}; ^1H NMR δ 7.47–7.11 (5 H, m), 6.34 (1 H, br s), 5.53 (2 H, d, J_{HP} = 11), 3.67 (6 H, d, J_{HP} = 12), 1.94 (3 H, d, J = 1), 1.91 (3 H, d, J = 1); ^{31}P NMR δ 4.3. Anal. Calcd for $C_{14}H_{20}NO_3PS$: C, 53.66; H, 6.43. Found: C, 53.70; H, 6.35.

Dimethyl *N*-((*cis*-3-acetyl-2,2-dimethylcyclobutyl)thioethanoyl)-*N*-methylphosphoramidate (6ga): yellow oil; 67% yield from **3g**; IR ν 2950, 2850, 1705, 1458 cm^{-1}; ^1H NMR δ 3.86 (3 H, d, J_{HP} = 11.6), 3.85 (3 H, d, J_{HP} = 11.6), 3.47 (3 H, d, J_{HP} = 6.8), 3.25 (1 H, dd, J = 14.8, 5.4), 3.09 (1 H, dd, J = 14.8, 8.8), 2.84 (1 H, dd, J = 10.1, 7.6), 2.63–2.51 (1 H, m), 2.15–1.85 (2 H, m), 2.04 (3 H, s), 1.35 (3 H, s), 0.90 (3 H, s); ^{31}P NMR δ 4.2. Anal. Calcd for $C_{13}H_{24}NO_4PS$: C, 48.59; H, 7.53. Found: C, 48.81; H, 7.56.

Dimethyl *N*-((*cis*-3-acetyl-2,2-dimethylcyclobutyl)thioethanoyl)-*N*-benzylphosphoramidate (6gb): yellow oil; 59% yield from **3g**; IR ν 3029, 2954, 2884, 1703, 1604, 1496, 1453, 1370, 1323, 1280, 1181, 1027, 846 cm^{-1}; ^1H NMR δ 7.31–7.21 (5 H, m), 5.53 (2 H, d, J_{HP} = 10.6), 3.71 (6 H, d, J_{HP} = 12), 3.17 (1 H, dd, J = 5.6, 15.2), 3.07 (1 H, dd, J = 8.4, 15.2), 2.84 (1 H, dd, J = 10.1, 7.6), 2.64 (1 H, m), 2.08 (1 H, m), 1.92 (1 H, m), 2.04 (3 H, s), 1.33 (3 H, s), 0.89 (3 H, s); ^{31}P NMR δ 4.6. Anal. Calcd for $C_{19}H_{28}NO_4PS$: C, 57.42; H, 7.10. Found: C, 57.40; H, 7.14.

Dimethyl *N*-(6-methoxy-6-oxothiohexanoyl)-*N*-methylphosphoramidate (6ha): yellow oil; 45% yield from **3h**; IR ν 2952, 2855, 1738, 1436, 1287, 1118, 1024, 847, 774 cm^{-1}; ^1H NMR δ 3.85 (6 H, d, J_{HP} = 12), 3.67 (3 H, s), 3.49 (3 H, d, J_{HP} = 7), 3.18 (2 H, t, J = 7), 2.35 (2 H, t, J = 7), 1.85 (2 H, p, J = 7), 1.70 (2 H, p, J = 7); ^{31}P NMR δ 4.3. Anal. Calcd for $C_{10}H_{20}NO_5PS$: C, 40.40; H, 6.78. Found: C, 40.16; H, 6.86.

Dimethyl *N*-(6-(diethylamino)-6-oxothiohexanoyl)-*N*-methylphosphoramidate (6ia): IR ν 2980, 2957, 1639 cm^{-1}; ^1H NMR δ 3.84 (6 H, d, J_{HP} = 11.7), 3.51 (3 H, d, J_{HP} = 7), 3.37 (2 H, q, J = 7.1), 3.31 (2 H, q, J = 7.1), 3.20 (2 H, m), 2.35 (2 H, m), 1.68 (4 H, m), 1.17 (3 H, t, J = 7.1), 1.10 (3 H, t, J = 7.1); ^{31}P NMR δ 4.1.

General Procedure for the Hydrolysis of Phosphoryl Thiocarbonyl Mixed Imides (6) To Form Thioamides (7). In a typical experiment, **6** (2.0 mmol) was dissolved in a mixture of THF (10 mL) and water (5 mL) and stirred at room temperature while monitoring the progress of the hydrolysis by TLC (silica gel, CH_2Cl_2, **7** has a higher R_f than **6**). When the hydrolysis was complete, the mixture was extracted with dichloromethane (4 × 10 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude thioamide was purified by vacuum liquid chromatography (VLC) on silica gel, eluting with 0–70% ethyl acetate/CH_2Cl_2. The major impurity was the corresponding carboxy amide which eluted more slowly. Isolated yields from the hydrolysis are given in Table I, and physical data on the thioamides synthesized are given below.

For hydrolysis in the presence of acid, **6** (2.0 mmol) was dissolved in a mixture of THF (10 mL) and aqueous HCl (5 mL, 1 M) and treated as above. Yields are given in parentheses in Table I.

***N*-Methylthioethanamide (7aa)**: light yellow solid; 94% yield from a neutral hyrolysis of **6aa**; mp 53–55 °C; IR ($CHCl_3$) ν 3408 (free NH), 3233 (H bonded NH), 2972, 1548, 1435, 1360, 1241, 1208, 1099, 951, 912, 688 cm^{-1}; ^1H NMR δ 8.20 (1 H, br s), 3.18 (3 H, d, J = 5), 2.61 (3 H, s); ^{13}C NMR δ 201.3, 33.4, 32.9. Anal. Calcd for C_3H_7NS: C, 40.41; H, 7.91. Found: C, 40.66; H, 7.91. (lit. mp,[35] ^1H NMR[36].)

***N*-Methylthiopropanamide (7ba)**: light yellow oil; 93% yield from an acidic hydrolysis of **6ba**; IR ν 3237, 2980, 2935, 1542, 1451, 1379, 1312, 1205, 1103, 1001, 953, 675 cm^{-1}; ^1H NMR δ 7.8 (1 H, br s), 3.18 (3 H, d, J = 5), 2.70 (2 H, q, J = 7.5), 1.31 (3 H, t, J = 7.5); ^{13}C NMR δ 207.5, 39.7, 32.9, 13.5. Anal. Calcd for C_4H_9NS: C, 46.56; H, 8.79. Found: C, 46.60; H, 9.00. (lit.[36] ^1H NMR.)

***N*-Benzylthiopropanamide (7bb)**: light yellow solid; 81% yield from an acidic hydrolysis of **6bb**; mp 40–41 °C; IR ν 3198, 3021, 2932, 2873, 1530, 1452, 1418, 1370, 1173, 1078, 1042, 758, 711, 694 cm^{-1}; ^1H NMR δ 7.30 (5 H, s), 4.83 (2 H, d, J = 5), 2.71 (2 H, q, J = 7), 1.37 (3 H, t, J = 7); ^{13}C NMR δ 206.6, 136.0, 128.7, 128.1, 127.9, 50.0, 39.7, 13.5. Anal. Calcd for $C_{10}H_{13}NS$: C, 66.99; H, 7.31. Found: C, 67.02; H, 7.14. (lit. mp,[37] ^1H NMR,[37] ^{13}C NMR[28]).

***N*-Methylthiobenzamide (7ca)**: yellow solid; 80% yield from a neutral hydrolysis of **6ca**; mp 75–76 °C; IR ν 3404, 3258, 3062, 2960, 2930, 2852, 1530, 1352, 1044, 909, 768, 734, 695 cm^{-1}; ^1H NMR δ 8.0 (1 H, br s), 7.77–7.17 (5 H, m), 3.20 (3 H, d, J = 5); ^{13}C NMR δ 199.7, 141.2, 130.8, 128.2, 126.5, 33.4. Anal. Calcd for C_8H_9NS: C, 63.54; H, 6.00. Found: C, 63.60; H, 6.20. (lit.[16] mp, ^1H NMR.)

***N*-Benzylthiobenzamide (7cb)**: light yellow solid; 78% yield from an acidic hydrolysis of **6cb**; mp 79–80 °C; IR ($CHCl_3$) ν 3390 (free NH), 3263 (H bonded NH), 3066, 3034, 2976, 2927, 2855, 1514, 1485, 1450, 1379, 1331, 947, 695 cm^{-1}; ^1H NMR δ 7.75–7.25 (5 H, m), 7.8 (1 H, br s), 7.35 (5 H, s), 4.99 (2 H, d, J = 5); ^{13}C NMR δ 199.1, 141.6, 136.2, 131.0, 128.9, 128.4, 128.2, 128.1, 126.6, 50.8. Anal. Calcd for $C_{14}H_{13}NS$: C, 73.97; H, 5.76. Found: C, 73.77; H, 5.96. (lit.[16] mp, ^1H NMR.)

***N*-Allylthiobenzamide (7cc)**: yellow oil; 95% yield from an acidic hydrolysis of **6cc**; IR ν 3245, 3029, 2916, 1644, 1518, 1487, 1449, 1376, 1322, 1284, 1220, 935, 770, 693 cm^{-1}; ^1H NMR δ 7.8 (1 H, br s), 7.73–7.29 (5 H, m), 5.95 (1 H, ddt, J = 17, 10, 6), 5.29 (1 H, dd, J = 17, 1), 5.24 (1 H, dd, J = 10, 1), 4.41 (2 H, dd, J = 6, 12); ^{13}C NMR δ 199.2, 141.6, 131.8, 130.9, 128.3, 126.8, 118.5, 48.9. Anal. Calcd for $C_{10}H_{11}NS$: C, 67.76; H, 6.25. Found: C, 68.00; H, 6.23.

***N*-Methyl-3,3-dimethylthiobutanamide (7da)**: yellow solid; 50% overall yield from **3d** using an acidic hydrolysis of unpurified **6da**; mp 43–45 °C; IR ν 3247, 2956, 2866, 1541, 1473, 1364, 1212, 1096, 1063, 1014 cm^{-1}; ^1H NMR δ 7.6 (1 H, br s), 3.18 (3 H, d, J = 5), 2.70 (2 H, s), 1.17 (9 H, s); ^{13}C NMR δ 203.4, 60.2, 32.9, 31.6, 29.7. Anal. Calcd for $C_7H_{15}NS$: C, 57.88; H, 10.41. Found: C, 58.00; H, 10.39.

***N*-Methyl-3-cyclopentylthiopropanamide (7ea)**: yellow oil; 84% yield from a neutral hydrolysis of **6ea**; IR ν 3228, 2947, 2865, 1544, 1452, 1376, 1214, 1088, 1040, 978 cm^{-1}; ^1H NMR δ 8.1 (1 H, br s), 3.17 (3 H, d, J = 4.8), 2.71 (2 H, t, J = 7.4), 1.78 (3 H, m), 1.6 (8 H, m); ^{13}C NMR δ 206.3, 45.9, 39.4, 35.9, 32.8, 32.4, 25.1. Anal. Calcd for $C_9H_{17}NS$: C, 63.10; H, 10.00. Found: C, 62.88; H, 9.81.

***N*-Methyl-3-methylthiobut-2-enamide (7fa)**: light yellow solid; 82% yield from a neutral hydrolysis of **6fa**; mp 46–48 °C; IR ($CHCl_3$) ν 3410 (free NH), 3253 (H bonded NH), 3053, 2976, 1644, 1522, 1449, 1358, 1330, 1225, 1176, 1040, 909, 750, 667 cm^{-1}; ^1H NMR δ 8.1 (1 H, br s), 6.08 (1 H, br s), 3.20 (3 H, d, J = 5), 2.00 (3 H, d, J = 1), 1.90 (3 H, d, J = 1); ^{13}C NMR δ 197.4, 141.2, 127.3, 32.0, 26.1, 19.7. Anal. Calcd for $C_6H_{11}NS$: C, 55.77; H, 8.58. Found: C, 55.82; H, 8.56.

***N*-Benzyl-3-methylthiobut-2-enamide (7fb)**: yellow oil; 98% yield from an acidic hydrolysis of **6fb**; IR ν 3230, 3030, 2972, 2913, 1643, 1520, 1496, 1454, 1373, 1324, 1147, 737, 698 cm^{-1}; ^1H NMR δ 7.4 (1 H, br s), 7.34 (5 H, s), 6.09 (1 H, br s), 4.85 (2 H, d, J = 5.3), 1.95 (3 H, d, J = 1.2), 1.80 (3 H, d, J = 1.2); ^{13}C NMR δ 197.1, 141.9, 136.3, 128.8, 128.3, 128.0, 127.8, 49.7, 26.4, 20.0. Anal. Calcd for $C_{12}H_{15}NS$: C, 70.20; H, 7.36. Found: C, 70.05; H, 7.46.

***N*-Methyl-(*cis*-3-acetyl-2,2-dimethylcyclobutyl)thioethanamide (7ga)**: white solid; 92% yield from a neutral hydrolysis of **6ga**; mp 104–105 °C; IR ($CHCl_3$) ν 3411 (free NH), 3302 (H bonded NH), 2959, 1697, 1530, 1464, 1372, 1227, 1215, 1184, 1156, 1082 cm^{-1}; ^1H NMR δ 8.2 (1 H, br s), 3.15 (3 H, d, J = 4.8), 2.93 (1 H, dd, J = 7.7, 10.2), 2.72 (1 H, m), 2.61 (2 H, m), 2.08 (3 H, s), 1.95 (2 H, m), 1.36 (3 H, s), 0.89 (3 H, s); ^{13}C NMR δ 207.9, 204.4, 53.99, 47.18, 43.53, 41.51, 32.65, 30.11 (2 C), 22.92, 17.47. Anal. Calcd for $C_{11}H_{19}NOS$: C, 61.93; H, 8.98. Found: C, 61.79; H, 8.75.

***N*-Benzyl-(*cis*-3-acetyl-2,2-dimethylcyclobutyl)thioethanamide (7gb)**: white solid; 80% yield from an acidic hydrolysis of **6gb**; mp 119–120 °C; IR ($CHCl_3$) δ 3391 (free NH), 3282 (H bonded NH), 3033, 2956, 1697, 1517, 1497, 1455, 1406, 1372, 1213, 1183, 1154, 780, 764, 738, 732, 668 cm^{-1}; ^1H NMR δ

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7.9 (1 H, br s), 7.3 (5 H, s), 4.81 (2 H, d, J = 5.3), 2.84 (1 H, dd, J = 7.8, 9.5), 2.70 (2 H, m), 2.59 (1 H, m), 1.95 (3 H, s), 1.92 (2 H, m), 1.33 (3 H, s), 0.84 (3 H, s); ^{13}C NMR δ 207.7, 203.9, 136.4, 128.9, 128.3, 128.0, 54.2, 50.2, 47.8, 43.6, 41.7, 30.3, 30.1, 23.1, 17.6. Anal. Calcd for $C_{17}H_{23}NSO$: C, 70.55; H, 8.01. Found: C, 70.52; H, 8.06.

***N*-Methyl-6-methoxy-6-oxothiohexanamide (7ha)**: light yellow oil; 86% yield from **6ha**; IR ν 3330, 2935, 1740, 1544, 1433, 1378, 1196, 1090, 1010 cm^{-1}; ^{1}H NMR δ 8.3 (1 H, br s), 3.68 (3 H, s), 3.17 (3 H, d, J = 4.7), 2.70 (2 H, t, J = 7.3), 2.37 (2 H, t, J = 7.2), 1.83 (2 H, m), 1.65 (2 H, m); ^{13}C NMR δ 205.0, 173.8, 51.2, 45.4, 33.3, 32.5, 28.2, 23.5. Anal. Calcd for $C_8H_{15}NO_2S$: C, 50.77; H, 7.99. Found: C, 50.54; H, 7.89.

***N*-Methyl-6-(diethylamino)-6-oxothiohexanamide (7ia)**: light yellow oil; 22% overall yield from **3i** using a neutral hydrolysis of unpurified **6ia**; IR ν 3248, 3076, 2975, 2935, 2874, 1619, 1560, 1463, 1381, 1267, 1218, 1097, 914, 730, 645 cm^{-1}; ^{1}H NMR δ 3.36 (2 H, q, J = 7.1), 3.32 (2 H, q, J = 7.1), 3.16 (3 H, d, J = 4.7), 2.75 (2 H, t, J = 7.0), 2.35 (2 H, t, J = 6.9), 1.81 (2 H, m), 1.68 (2 H, m), 1.18 (3 H, t, J = 7.1), 1.11 (3 H, t, J = 7.1); ^{13}C NMR δ 205.1, 172.2, 45.4, 42.0, 40.2, 32.7, 32.5, 28.4, 23.9, 14.1, 12.9. Anal. Calcd for $C_{11}H_{22}N_2OS$: C, 57.35; H. 9.63. Found: C, 57.36; H. 9.45.

Control Experiment. By the general procedure given above, **6fb** was hydrolyzed in aqueous THF for 2 days at room temperature. Workup of one-third of the reaction mixture produced an oil which was shown by ^{1}H NMR to consist of carboxamide **9fb** and thioamide **7fb** in a 56:44 molar ratio. After an additional 2 days (4 days total) workup of half of the remaining reaction mixture and subsequent ^{1}H NMR analysis showed no change in the molar ratio. At this point, pure thioamide **7fb** was added to the remaining reaction mixture and stirred an additional 2 days at room temperature. Subsequent analysis after workup indicated that none of the excess thioamide **7fb** was converted to amide **9fb**.

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Registry No. **1g**, 61826-55-9; **1h**, 627-91-8; **1i**, 91017-35-5; **2a**, 74-89-5; **2b**, 100-46-9; **2c**, 107-11-9; **3a**, 75-36-5; **3b**, 79-03-8; **3c**, 98-88-4; **3d**, 7065-46-5; **3e**, 104-97-2; **3f**, 3350-78-5; **3g**, 130062-20-3; **3h**, 35444-44-1; **3i**, 64792-78-5; **4a**, 31464-99-0; **4b**, 130012-35-0; **4c**, 36592-38-8; **5aa**, 130012-36-1; **5ba**, 130012-37-2; **5bb**, 130012-38-3; **5ca**, 123269-09-0; **5cb**, 130012-39-4; **5cc**, 130012-40-7; **5da**, 130012-41-8; **5ea**, 130012-42-9; **5fa**, 130012-43-0; **5fb**, 130012-44-1; **5ga**, 130012-45-2; **5gb**, 130012-46-3; **5ha**, 130012-47-4; **5ia**, 130012-48-5; **6aa**, 130012-49-6; **6ba**, 130012-50-9; **6bb**, 130012-51-0; **6ca**, 123269-11-4; **6cb**, 130012-52-1; **6cc**, 130012-53-2; **6da**, 130012-54-3; **6ea**, 130012-55-4; **6fa**, 130012-56-5; **6fb**, 130012-57-6; **6ga**, 130012-58-7; **6gb**, 130012-59-8; **6ha**, 130012-60-1; **6ia**, 130012-61-2; **7aa**, 5310-10-1; **7ba**, 2955-71-7; **7bb**, 63418-53-1; **7ca**, 5310-14-5; **7cb**, 14309-89-8; **7cc**, 130012-62-3; **7da**, 130012-63-4; **7ea**, 130012-64-5; **7fa**, 130012-65-6; **7fb**, 130012-66-7; **7ga**, 130012-67-8; **7gb**, 130012-68-9; **7ha**, 130012-69-0; **7ia**, 130031-61-7; $(MeO)_2P(S)Cl$, 2524-03-0.

Intra- and Intermolecular α-Sulfamidoalkylation Reactions

Chai-Ho Lee† and Harold Kohn*

Department of Chemistry, University of Houston, Houston, Texas 77204-5641

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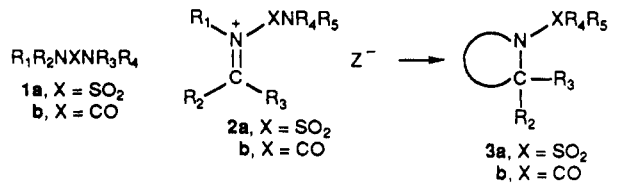
The utility of α-sulfamidoalkylation processes for the generation of sulfamides has been examined. Select aryl-substituted sulfamides were prepared and then treated with acid. Both intra- and intermolecular α-sulfamidoalkylation transformations were observed to proceed in moderate to good yields. The pathways for these reactions are discussed. The generality of these processes has been demonstrated using *N*,*N*′-di(aryl-substituted)sulfamides, and the utility of these reactions was examined for the preparation of cyclic sulfamides of novel structure.

In recent years an increasing number of articles has appeared describing the synthesis, properties, and biological activities of substituted sulfamides **1a**.[1] These compounds are the sulfonyl analogues of ureas **1b**. Previously, we have demonstrated that intramolecular α-ureidoalkylation transformations proceeding through the intermediacy of an iminium ion (i.e., **2b**) provide an expeditious route for the preparation of N,N-cycloalkylated ureas (i.e., **3b**).[2] In the present study, we report on the use of the corresponding α-sulfamidoalkylation process (i.e., **2a** → **3a**) for the generation of sulfamides of novel structure.



Results and Discussion

α-Sulfamidoalkylation Reactions of Sulfamide and *N*-Mono(aryl-substituted)sulfamides. The utility of the proposed α-sulfamidoalkylation transformation **2a** → **3a** was assessed by using sulfamide **4** and the aryl-substituted sulfamides **5** in which the number of methylene units separating the aromatic ring from the sulfamide moiety was systematically varied from zero to four. The starting sulfamides **5a–e** were prepared according to established synthetic protocols.[3] Iminium ion formation was

† Present Address: Department of Chemistry, Won Kwang University, Iri, Chun-Buck, Korea.

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