**O-Benzylcryptaustoline, 10.** 7-(Benzyloxy)-6-methoxyisoquinoline with the formamidine 8 (0.12g, 0.26 mmol) in place[14] was introduced into a 100-mL flame-dried round-bottomed flask equipped with a magnetic stirrer. Tetrahydrofuran (50 mL) was added and the mixture cooled to −78 °C. The system was purged with argon following which *sec*-butyllithium (0.23 mL, 1.28 M, 0.29 mmol) was added dropwise over 15 min. The dark red solution was stirred an additional 20 min, and 2-chloro-4,5-dimethoxybenzyl bromide[13] (0.084 g, 0.32 mmol) in 5 mL of tetrahydrofuran was rapidly injected. The solution immediately turned clear, and after 10 min of additional stirring an additional 2 equiv of *sec*-butyllithium (0.46 mL, 1.28 M, 0.58 mmol) was added dropwise to the solution. Following 10 min of stirring, 1 equiv of $NH_4Cl$ was added and the mixture warmed to rt. An aliquot of the cyclized amine was isolated for spectral evaluation and gave the following: mp 131–133 °C dec. $^1H$ NMR ($CDCl_3$): δ 7.39 (s, 1 H); 6.69 (s, 2 H); 6.50 (s, 2 H); 6.30 (s, 1 H); 5.12 (s, 2 H); 4.81–4.69 (1 H, q); 3.84 (s, 3 H); 3.78 (s, 3 H); 3.73 (s, 3 H); 3.60–2.80 (m, 6 H). $^{13}C$ NMR: δ 148.23; 148.18; 147.64; 146.14; 137.32; 130.64; 128.83; 128.48; 128.02; 127.75; 127.36; 127.23; 114.17; 112.91; 112.70; 112.28; 71.42; 56.15; 56.12; 55.97; 55.24; 40.49; 40.21; 29.51. IR $cm^{-1}$: 2931; 1606; 1508; 1219; 861. To complete the synthesis, excess methyl iodide (1.056 mmol, 4 equiv) was added and the flask placed in the freezer (−20 °C) for 1 week. The product, **10**, was collected as an off-white solid in 58% yield, mp 231–233 °C dec (lit.[17] mp 224–226 °C dec). $[\alpha]_D$: +48.5° (*c* 1.0, acetone), compared to material form another route[13] $[\alpha]_D$ +47.8° (*c* 0.8, acetone). The material was debenzylated following the procedure of Kametani and Ogasawara[17] to give the alkaloid $[\alpha]_D$ +141° (*c* 0.6, ethanol); natural material $[\alpha]_D$ −150° (*c* 0.4, ethanol).[17] The optical rotation indicated that the synthetic material had an ee of 94%.

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**Supplementary Material Available:** Experimental details and physical properties of the precursors to **6** and a $^1H$ or $^{13}C$ NMR spectrum of each indoline compound (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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# Preparation of Pyrrolo[2,1-*b*][1,3]benzothiazin-9-ones via Intramolecular Sulfenylation of an *N*-Acylpyrrole[1]

Kelley A. Tafel and Dallas K. Bates*

*Department of Chemistry, Michigan Technological University, Houghton, Michigan 49931*

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Pyrrolo[2,1-*b*][1,3]benzothiazin-9-one (**6a**) was synthesized in 45% overall yield from thiosalicylic acid in six steps. The title compound (88%) and its 1-trifluoroacetyl (83%) and 1-formyl derivatives were synthesized via intramolecular reaction of 1-(2-ethylsulfinyl)benzoylpyrrole (**5**) by thermal cyclization or treatment with trifluoroacetic anhydride or DMF/$POCl_3$, respectively. The key step in each case is formation of the heterocycle by sulfoxide activation followed by C–S bond formation via attack *at sulfur*. Reaction of **6a** with common electrophiles (trifluoroacetic anhydride (86%), $POCl_3$/DMF (75%), and acetyl nitrate) indicates that C-1 is the predominant site of electrophilic substitution.

## Introduction

The reaction of indole and pyrrole with electrophilic sulfur species to form C–S bonds is well-documented. Alkylthio[2] groups have been introduced into these systems using the original Swern reagent (prepared from DMSO/trifluoroacetic anhydride[3]) and the original Corey–Kim reagent (prepared from *N*-chlorosuccinimide/dimethyl sulfide[4]) or related reagents.[5] Arenesulfenyl iodides, formed in situ from aromatic thiols and $KI/I_2$, react with pyrroles (highly substituted to avoid ring iodination) to give pyrrolyl aryl sulfides.[6] For example, methyl 2-mercaptobenzoate in the presence of 2,4-dimethyl-3-pyrrolecarboxylic acid ethyl ester gave the precursor to the only reported pyrrolo[2,1-*b*][1,3]benzothiazin-9-one derivative (1).[6]

Intramolecular capture of electrophilic sulfur species has been exploited in the synthesis of fused heteroaromatic systems. Oxidative cyclization of arylthioureas to 2-aminobenzothiazoles has been accomplished by sulfur activation via treatment with bromine[7,8] or inorganic halides (thionyl chloride;[9] sulfuryl chloride[10]). This methodology has been extended to substituted 3-thienylthioureas and pyrazolylthioureas to afford thienyl[3,2-*d*]thiazoles[11a] and pyrazolo[3,4-*d*]thiazoles,[11b] respectively. In addition, *N*-arylbenzamidines can be converted to 1,2,4-benzothiadiazines upon treatment with *N*-chlorosuccinimide and 4,4′-thiobis(morpholine).[12]

A major problem in using positive halogen species to activate thiols or sulfides for intramolecular sulfenylation

(1) Part 4 of the series Intramolecular Capture of Pummerer Rearrangement Intermediates; for part 3 see ref 13a.
(2) (a) Franco, F.; Greenhouse, R.; Muchowski, J. *J. Org. Chem.* **1982**, *47*, 1682–1688. (b) Hartke, K.; Strangemann, D. *Heterocycles* **1986**, *24*, 2399–2402.
(3) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957–962.
(4) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586–7587.
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(11) (a) Grehn, L. *J. Heterocycl. Chem.* **1978**, *15*, 81. (b) Eilingsfeld, H.; Niess, R. Ger. Offen., 2,429,195; *Chem. Abstr.* **1976**, *84*, 135649y.
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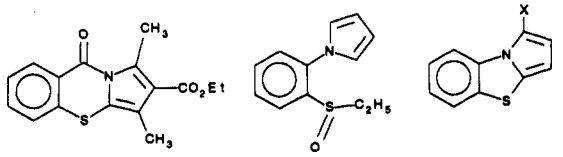
0022-3263/92/1957-3676$03.00/0 

is that these reagents may preferentially react with electron-rich heteroaromatic systems. To avoid this problem, we have investigated sulfoxides as the source of the sulfenylating agent. Thus pyrrolo[2,1-*b*]benzothiazole **3a** was prepared in high yield from sulfoxide **2** by treatment with trifluoroacetic anhydride (TFAA).[13a] This cyclization can also be effected by treatment of **2** with Vilsmeier–Haack reagent ($POCl_3$/DMF[13b]), which serves to both activate the sulfoxide and to functionalize the derived heterocycle, producing benzothiazole **3b** in a one-pot sequence.



1 2 3a X = H; b X = CHO

As part of a program to apply this methodology toward preparation of new N,S-heterocycles, the pyrrolo[2,1-*b*]-[1,3]benzothiazin-9-one system was an appealing target. Although cyclization at sulfur of sulfoxide **5** appeared favorable due to the formation of a 6-membered ring, it was not clear that there would be sufficient rotational freedom about the acyl–phenyl bond and/or the N–acyl bond to allow cyclization. The rotational barrier about the acyl–phenyl bond could lock the molecule into a conformation in which the pyrrole ring and the sulfur atom are too far apart for reaction. Also, the known considerable rotational barrier about pyrrole N–acyl bonds[14] could lock the pyrrole and phenyl rings into relatively coplanar positions, where the pyrrole $\pi$ electrons and the sulfoxide sulfur could not interact.

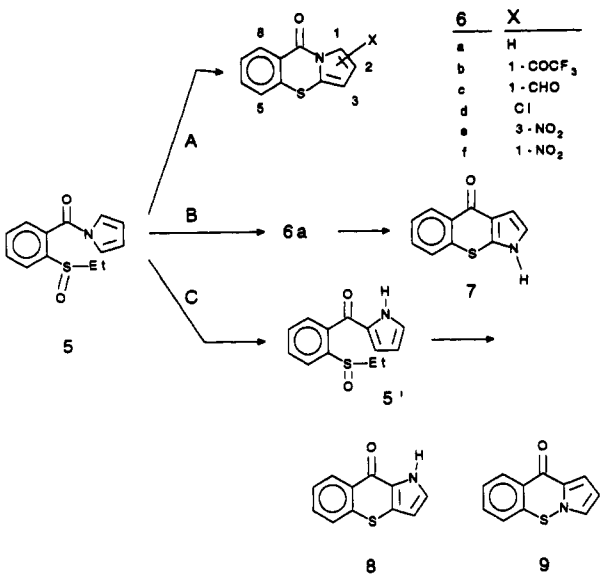
The small body of literature on *N*-acylpyrroles contains conflicting reports regarding the stability of this functionality: While simple *N*-acylpyrroles, such as 1-acetyl and 1-benzoyl pyrrole, have been used as acylating agents,[15a] these compounds exhibit excellent thermal stability as evidenced by purification by vacuum distillation at relatively high temperatures.[16] It thus seemed possible that the *N*-acylpyrrole sulfoxide **5**, if it cyclized at all, could conceivably travel three different reaction paths (Scheme I): (A) direct sulfenylation to **6a**, (B) cyclization to **6a**, followed by intramolecular migration of the acyl group to give **7**, or (C) transacylation to **5′**, followed by sulfenylation to produce **8** and/or **9**. None of these systems has been reported previously.

We report here a general synthesis of pyrrolo[2,1-*b*]-[1,3]benzothiazin-9-ones via direct intramolecular capture of various electrophilic sulfur species (path A).

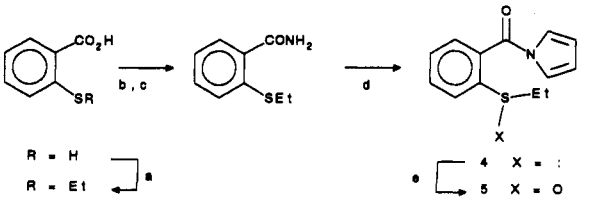
## Results and Discussion

Sulfoxide **5** was synthesized as outlined in Scheme II. Commercially available thiosalicylic acid was S-ethylated[17] and converted to the amide in the usual manner.[17] Subsequent "capping" of the amide via the method of Lee et al.[15a] to the *N*-acylpyrrole **4** followed by oxidation by a multiphase reaction using sodium metaperiodate in a water/methanol/methylene chloride system gave **5** in an overall yield of 51%.

**Scheme I**




**Scheme II**[a]




[a] (a) $C_2H_5Br$, KOH, EtOH; (B) $SOCl_2$, PhH; (c) $NH_4OH$; (d) 1,4-dichloro-1,4-dimethoxybutane; (e) $NaIO_4$, $H_2O$, MeOH, $CH_2Cl_2$.

Sulfoxide **5** was cyclized under three conditions. Thermal activation[18] seemed to present a good possibility for cyclization because the high temperature would offer the greatest rotational freedom. Refluxing **5** in *p*-xylene gave **6a** in 88% yield after 7 h. In contrast to reactions promoted by TFAA and other electrophilic reagents discussed below, thermal cyclization does not lead to ring substitution of the newly formed heterocycle through exposure to excess activating agent. Prolonged reflux in benzene or toluene left **5** unchanged.

The structure of **6a** was assigned on the basis of spectroscopic data. The infrared spectrum showed a carbonyl absorption at 1695 $cm^{-1}$, indicating the acylpyrrole functionality.[19] The $^1H$ NMR spectrum indicated the absence of the ethyl side chain of **5** and the presence of only three pyrrole protons. These data, together with the mass spectrum which showed a molecular ion at $m/z$ 201 and detailed $^{13}C$ NMR spectral analysis, clearly establish the structure for **6a** as pyrrolo[2,1-*b*][1,3]benzothiazin-9-one.

The assignment of pyrrole protons was possible by analysis of the NMR splitting patterns and chemical shifts. One of the pyrrole protons had been shifted downfield considerably to 7.92 ppm, which was a good indication that it had been placed in the deshielding region of the carbonyl group as a consequence imposed by the conformational constraints of cyclization. The only pyrrole proton which could experience this effect is H-1. This peak appears as

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(17) Oae, S.; Numata, T. *Tetrahedron* **1974**, *30*, 2641–46.

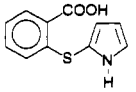
(18) Bates, D. K. *J. Org. Chem.* **1977**, *42*, 3452–54.

(19) Migration of the aroyl group to C-2 or C-3 is ruled out, as the carbonyl stretch for 2-aroyl and 3-aroyl pyrroles is approximately 85 and 60 $cm^{-1}$ lower, respectively, than the value observed here (Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*; Academic Press: London, 1977, p 284).

a doublet of doublets with $J$ = 1.59 and 3.39 Hz. These values also support the assignment of the 7.92 ppm peak to H-1 and allow unambiguous assignment of the other two pyrrole protons. The 1.59 Hz value is typical of "meta" (between positions 2 and 4) pyrrole coupling, indicating that the doublet of doublets at 6.39 ppm ($J$ = 1.59, 3.39 Hz) must be due to H-3. H-1 and H-3 couple to H-2 equally (3.39 Hz), resulting in a triplet at 6.60 ppm. These NMR data specifically rule out the possible alternate structures **7** and **8** for the cyclization product.

$^{13}C$ NMR spectral data are also in agreement with structure **6a**. A low intensity peak at 157.7 ppm, a quaternary carbon according to the attached proton test (APT), supported the presence of an *amide* carbonyl carbon (C-10). This information helps rule out alternate structures **7**, **8**, and **9**, which all contain *ketone* carbonyl carbons that would appear at approximately 180–210 ppm. The APT also showed the carbon atoms at 134.8, 121.1, and 118.9 ppm to be quaternary. These data, along with information obtained from a 2-D carbon–carbon shift correlation (INADEQUATE) experiment, were used to unambiguously assign all of the $^{13}C$ NMR peaks (see Experimental Section).

In addition to the $^{13}C$ NMR spectral data, chemical means were also employed to rule out alternate structures. When product **6a** was boiled for 2.5 h in a 10% $K_2CO_3$ solution and then acidified, a white solid was obtained whose infrared spectrum (3380, 3350, 3140–2500 (broad) $cm^{-1}$) and mass spectrum ($M^+ = m/z$ 219) clearly showed it to be the "ring-opened" carboxylic acid **10**. System **6** could form this acid much more readily than compounds **7**, **8**, and/or **9**. Treatment of **10** with dicyclohexylcarbodiimide in refluxing toluene reformed **6a** in poor yield (20%). Although compound **6a** underwent ring opening under alkaline conditions, it was quantitatively recovered after refluxing for 24 h with 2 equiv of trifluoroacetic acid in toluene.

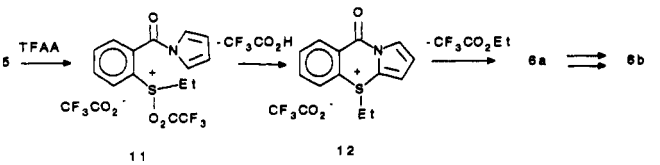



10

TFAA in methylene chloride also promoted cyclization. Treatment of sulfoxide **5** with a large excess (3.7 equiv) of TFAA in the presence of pyridine as an acid scavenger[20] at room temperature for several hours gave 1-(trifluoroacetyl)pyrrolo[2,1-*b*][1,3]benzothiazin-9-one (**6b**) in 83% yield. We suggest that sulfoxide **5** forms a (trifluoroacetoxy)sulfonium salt, **11**, which after attack of pyrrole at sulfur gives intermediate **12** (Scheme III). Compound **6a** is formed as the ethyl side chain is displaced in situ by the trifluoroacetate ion, producing $CF_3CO_2Et$, which is removed from the product mixture during workup. Compound **6b** results from the reaction of **6a** with excess TFAA. Both H-2 and C-2 peaks in the respective NMR spectra of **6b** are coupled to fluorine; a complete analysis of $^{13}C$–$^{19}F$ and $^{1}H$–$^{19}F$ coupling in (trifluoroacetyl)pyrroles will be published separately.

In an attempt to produce the unsubstituted parent compound **6a** using TFAA, **5** was treated with a slight excess of TFAA (1.3 equiv) in the presence of pyridine at 0 °C for 40 min. However, the reaction was not selective: The reaction mixture contained the unsubstituted compound **6a** and the 1-trifluoroacetylated compound **6b** as well as unreacted starting material.

**Scheme III**




The Vilsmeier–Haack reagent ($POCl_3$/DMF) was not effective for cyclization. Sulfoxide **5** under conditions used previously[13b] gave three products in poor yield: 1-aldehyde **6c**, sulfide **4** (from sulfoxide deoxygenation as previously observed[13b]), and an unstable chlorinated heterocycle **6d**, which decomposed upon standing. Chlorination of heteroaromatics[21] by positive halogen sources (such as the Swern reagent, prepared from DMSO and $(COCl)_2$[22]) is well-known. Clearly sulfoxide cyclization to 1-formylpyrrolo[2,1-*b*][1,3]benzothiazin-9-one is not a synthetically viable process.

On the other hand, **6a** under Vilsmeier–Haack formylation conditions[13b] gave **6c** in 75% yield after recrystallization. The infrared spectrum of **6c** showed two carbonyl absorptions (1685 and 1645 $cm^{-1}$), the mass spectrum indicated a molecular ion at $m/z$ 229, and an aldehydic proton appeared as a singlet at 10.62 ppm in the NMR spectrum. Assignment of the aldehyde group to the 1-position was based on NMR spectral data. The NMR spectrum of **6c** showed H-1 to be absent, while the doublet of H-2 has been shifted downfield to 7.52 ppm. A coupling constant of 4.16 Hz was observed for the two pyrrole doublets, again indicating coupling between H-2 and H-3 (1-substitution) rather than between H-1 and H-2 (3-substitution).

Although no 3-isomer was isolated from this reaction, a small spot suspected of being this isomer appeared slightly above the spot from **6c** by TLC. However, the substance was present in such small amounts that it could not be isolated.

Under the nitration conditions of Bray,[20] two products of very similar $R_f$ were obtained in low yield. A small amount of the product with the higher $R_f$ was isolated after preparative TLC and identified as the 3-nitro derivative **6e** by NMR and mass spectral data. Substitution at the 3-position was indicated by the presence of a doublet at 7.93 ppm which strongly suggests that the H-1 proton is present (the signal for H-1 of **6a** is at 7.92 ppm). The other pyrrole proton signal appears as a doublet at 7.18 ppm, having been shifted downfield from the position of both H-2 and H-3 in **6a** presumably due to the nitro substituent. This peak is assigned to H-2 because the coupling constant of 3.84 Hz is indicative of $H_\alpha$–$H_\beta$ coupling in fused pyrroles and therefore 3-nitro substitution.

Although the lower $R_f$ compound could not be isolated in pure form, analysis of the $^1H$ NMR spectrum of the mixture indicated that it is the 1-isomer **6f**. The two pyrrole protons of **6f** appeared as doublets at 6.39 ppm and 7.42 ppm with coupling constants of 4.19 Hz, indicative of pyrrole $H_\beta$–$H_\beta$ coupling and 1-substitution. As with the 3-isomer, the proton "adjacent" to the nitro group, H-2, has been shifted downfield approximately 0.8 ppm from its position in **6a** by the nitro group. Mass spectral analysis of the mixture showed only mononitration products.

In general, the reactivity of **6a** parallels that of **3a**.[13] The dominating sulfur substituent directs substitution to C-1

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(22) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.

while the carbonyl group only mildly deactivates the pyrrole ring.

## Conclusions

In spite of the reported facility of *N*-acylpyrroles as acylating agents,[15a] the N–acyl bond in all the pyrroles reported here is remarkably stable. Rotational barriers about the phenyl–acyl and N–acyl bonds of **5** are not sufficiently restrictive to prevent interaction of the sulfoxide and pyrrole moieties as evidenced by the variety of successful cyclization conditions. The synthesis of pyrrolo[2,1-*b*][1,3]benzothiazin-9-one **6a** exemplifies a useful approach to *intramolecular* capture of an electrophilic sulfur species generated from sulfoxides.

## Experimental Section

Melting points are reported uncorrected. NMR spectra were recorded at 200 or 300 MHz ($^1$H) or 75 MHz ($^{13}$C) in $CDCl_3$ solutions unless otherwise specified. Elemental analyses were performed by Spang Microanalytical Laboratory in Eagle Harbor, MI.

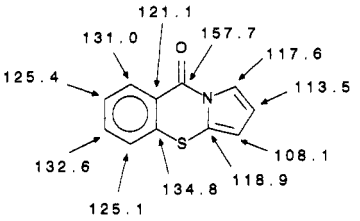
2-(Ethylthio)benzoic acid was prepared in 84% yield, mp 136–137 °C (lit.[17] mp 134–135 °C). 2-(Ethylthio)benzamide was prepared in 83% yield, mp 136 °C (lit.[17] mp 130–131 °C).

**1-[2-(Ethylthio)benzoyl]pyrrole (4).** To a stirred suspension of 2-(ethylthio)benzamide (9.1 g, 50.2 mmol) in $CH_3CN$ (250 mL) was added 1,4-dichloro-1,4-dimethoxybutane (11.3 g, 60.2 mmol, 1.2 equiv, prepared according to Chan and Lee[15b]) dropwise over 2 min. The solid dissolved to give a clear yellow solution to which Amberlyst A-21 resin (25 g) was added in portions. The solution was heated at 55–60 °C for 18 h. The black solution was then filtered and the solvent evaporated in vacuo to give 11.95 g of a crude black oil, which was flash chromatographed ($CHCl_3$) to give 10.81 g (93%) of a gold liquid, **4**: IR (neat) 1700 cm$^{-1}$; $^1$H NMR $\delta$ 7.67–7.25 (m, 4 H), 7.15 (t, $J$ = 2.4 Hz, 2 H), 6.3 (t, $J$ = 2.4 Hz, 2 H), 2.9 (q, $J$ = 7.4 Hz, 2 H), 1.25 (t, $J$ = 7.4 Hz, 3 H); MS [$m/z$ (relative intensity)] 231 ($M^+$, 65), 202 (4.1), 165 (42.8), 137 (23.2), 135 (60.4), 109 (46.5).

**1-[2-(Ethylsulfinyl)benzoyl]pyrrole (5).** A two-phase mixture of **4** (13.02 g, 56.3 mmol) in $CH_2Cl_2$ (60 mL) and $NaIO_4$ (16.83 g, 78.7 mmol, 1.4 equiv) in $H_2O$ (60 mL) and MeOH (100 mL) was stirred vigorously for 2 days, at which time a thin-layer chromatogram of the product mixture showed only a trace of starting material remaining. The mixture was vacuum filtered and the filter cake rinsed with $CH_2Cl_2$. To the combined filtrate and rinse were added 75 mL of $H_2O$ and 25 mL of $CH_2Cl_2$, and the resulting layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (1 × 75 mL) and the combined organics were washed (2 × 75 mL) with $H_2O$ and dried over $Na_2SO_4$. After evaporating the solvent in vacuo, a crude orange oil (14.27 g) was obtained. Flash chromatography ($CHCl_3$) of this oil yielded a light gold oil which solidified upon standing to an off-white solid, **5**, 10.98 g (79%), mp 48–53 °C. This solid is used without further purification in subsequent reactions; however, analytically pure material may be obtained by recrystallization from EtOAc/hexanes (mp 54–56 °C): IR (neat) 1700, 1075, 1045 cm$^{-1}$; $^1$H NMR $\delta$ 8.18 (d, $J$ = 7.79 Hz, 1 H), 7.82–7.73 (m, 1 H), 7.61–7.56 (m, 2 H), 7.13 (t, $J$ = 2.3 Hz, 2 H), 6.32 (t, $J$ = 2.3 Hz, 2 H), 3.15 (dq, $J$ = 7.46, 13.27 Hz, 1 H), 2.82 (dq, $J$ = 7.46, 13.27 Hz, 1 H), 1.27 (t, $J$ = 7.46 Hz, 3 H); MS [$m/z$ (relative intensity)] 247 ($M^+$, 0.3), 231 (0.5), 181 (98.4), 153 (100). Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30; N, 5.66. Found: C, 63.15; H, 5.27; N, 5.72.

**Cyclization of 5: Pyrrolo[2,1-*b*][1,3]benzothiazin-9-one (6a) and 1-(Trifluoroacetyl)pyrrolo[2,1-*b*][1,3]benzothiazin-9-one (6b). Method A: Thermal.** A stirred solution of **5** (7 g, 28.3 mmol) in *p*-xylene (320 mL) was refluxed until no more starting material was detected by TLC (7 h). The solution darkened progressively from pale yellow to dark green-brown. The solvent was evaporated in vacuo to give a crude dark green solid. After column chromatography ($CHCl_3$), 5.0 g (88%) of a bright yellow solid, **6a**, (mp 118–122 °C) was obtained. A small amount of this solid was recrystallized from hexanes for analysis, mp 120–123 °C: IR (KBr) 1695 cm$^{-1}$; $^1$H NMR $\delta$ 8.53 (dd, $J$ = 1.50, 8.0 Hz, 1 H), 7.92 (dd, $J$ = 1.59, 3.39 Hz, 1 H), 7.53 (ddd, $J$ = 1.50, 7.62, 8.37 Hz, 1 H), 7.41–7.32 (m, 2 H), 6.60 (t, $J$ = 3.39 Hz, 1 H), 6.39 (dd, $J$ = 1.59, 3.39 Hz, 1 H); MS [$m/z$ (relative intensity)] 201 ($M^+$, 100), 172 (23), 169 (7), 146 (37), 77 (4). Anal. Calcd for $C_{11}H_7NOS$: C, 65.65; H, 3.51; N, 6.96. Found: C, 65.79; H, 3.60; N, 6.87.

$^{13}$C NMR data for **6a** ($CDCl_3$):




**Method B: Trifluoroacetic Anhydride (TFAA). Large Excess of TFAA.** To an ice-cold solution of TFAA (1.9 mL, 14.9 mmol, 3.7 equiv) in $CH_2Cl_2$ (25 mL) was added pyridine (1.27 g, 4 equiv). After stirring 5 min on the ice bath, a colorless solution of **5** (1.0 g, 4 mmol) in $CH_2Cl_2$ (6 mL) was added dropwise over 5 min with external cooling. After addition was complete, the bright yellow-green reaction mixture was stirred at 0 °C for an additional 15 min and then at room temperature for 3.5 h, at which time it was poured into a 5% $NaHCO_3$ solution (50 mL) and stirred for 5 min. The two layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 50 mL). The combined organics were washed with 5% $NaHCO_3$ solution (2 × 50 mL) and dried over $Na_2SO_4$, and the volatiles were removed in vacuo to give a wet yellow solid (1.04 g) which smelled strongly of pyridine. Chromatography ($CHCl_3$) of the crude solid yielded a light yellow solid, **6b**, 0.97 g, (83%): mp 144–148 °C; IR (KBr) 1715, 1685 cm$^{-1}$; $^1$H NMR $\delta$ 8.52 (dd, $J$ = 1.30, 8.14 Hz, 1 H), 7.70–7.65 (m, 1 H), 7.54–7.47 (m, 3 H), 6.51 (d, $J$ = 4.21 Hz, 1 H); $^{13}$C NMR ($CDCl_3$/DMSO-$d_6$) $\delta$ 170.2 (q, $J$ = 37 Hz), 157.6, 133.8, 133.3, 132.9, 131.6, 127.2, 127.07 (m), 126.3, 125.3, 122.5, 116.5 (q, $J$ = 291 Hz), 108.6; MS [$m/z$ (relative intensity)] 297 ($M^+$, 23.9), 228 (100), 172 (43), 145 (32.7). Anal. Calcd for $C_{13}H_6NO_2SF_3$: C, 52.52; H, 2.03; N, 4.71. Found: C, 52.55; H, 2.16; N, 4.80.

**Slight Excess of TFAA.** To an ice-cold mixture of $CH_2Cl_2$ (15 mL) and TFAA (0.37 mL, 2.6 mmol, 1.3 equiv) was added pyridine (0.24 mL, 3 mmol, 1.5 equiv). After stirring for several minutes, a colorless solution of **5** (0.5 g, 2 mmol) in $CH_2Cl_2$ (4 mL) was added dropwise with stirring over 3 min with external cooling. The mixture was stirred at 0 °C for 40 min, at which time TLC (1:1 $CHCl_3$/hexanes) showed the reaction mixture to contain unsubstituted heterocycle **6a**, trifluoroacetylated heterocycle **6b**, and starting material **5**. The workup was similar to that described above and yielded 0.54 g of a crude wet dark gold solid that smelled strongly of pyridine. This crude solid was chromatographed (1:3 $CHCl_3$/hexanes) to obtain 0.23 g (1.1 mmol, 55%) of **6a** (by TLC and NMR), 0.05 g (0.2 mmol, 10%) of **6b** (by TLC), and trace amounts of sulfoxide **5** (by TLC).

**Method C: Vilsmeier–Haack Reagent ($POCl_3$/DMF).** To stirred DMF (5 mL) at 0 °C was added neat $POCl_3$ (0.7 mL, 7.5 mmol, 2.5 equiv) via syringe. After stirring for 40 min at 0 °C, a solution of **5** (0.75 g, 3 mmol) in DMF (20 mL) was added dropwise over 15 min with stirring and external cooling. The reaction mixture was stirred at 0 °C for an additional 30 min and then at room temperature for 2.75 h. The dark amber mixture was dumped into 150 mL of $H_2O$ and the pH was adjusted to 7 with a 4 M sodium acetate solution. The milky yellow mixture was stirred for 30 min at room temperature while a yellow solid precipitated. Vacuum filtration gave 1.50 g of wet solid, which showed 3 spots on TLC ($CHCl_3$). Preparative TLC ($CHCl_3$) of a small sample was done but gave poorly resolved bands having mass and NMR spectra indicative of **6d** and **4** in the highest $R_f$ band, followed by pure **4** in the second band and **6c** as the most polar component (see spectral data and analyses below).

**Formylation of 6a: 1-Formylpyrrolo[2,1-*b*][1,3]benzothiazin-9-one (6c).** To stirred DMF (8 mL) at 0 °C was added neat $POCl_3$ (0.65 mL, 7 mmol, 1.4 equiv) via syringe. After stirring for 40 min at 0 °C, a solution of **6a** (1.0 g, 5 mmol) in DMF (35 mL) was added dropwise over 10 min with stirring and external cooling. The reaction mixture was stirred at 0 °C for an additional 15 min, heated slowly to 70 °C in a water bath over 30 min, and

then maintained at this temperature for 2.5 h. The dark amber mixture was dumped onto 300 mL of crushed ice. The pH was adjusted to 8 using a 4 M NaOAc solution. A light green precipitate formed during and after this addition. After stirring at room temperature for 24 h, the solid was collected by vacuum filtration. Recrystallization (EtOAc/hexanes) of the crude solid yielded 0.86 g (75%) of a dull gold solid, **6c**, mp 194–195 °C: IR (KBr) 1685, 1645 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) $\delta$ 10.62 (s, 1 H), 8.5 (dd, $J$ = 0.75, 8.16 Hz, 1 H), 7.84–7.81 (m, 2 H), 7.64–7.61 (m, 1 H), 7.52 (d, $J$ = 4.16 Hz, 1 H), 6.86 (d, $J$ = 4.16 Hz, 1 H); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 180.9, 159.3, 135.4, 134.0, 133.2, 130.8, 128.6, 127.0, 125.8, 121.6, 121.5, 109.6; MS [$m/z$ (relative intensity)] 229 ($M^+$, 100), 201 (34.3), 172 (45.6). Anal. Calcd for $C_{12}H_7NO_2S$: C, 62.87; H, 3.08; N, 6.11. Found: C, 62.81; H, 3.21; N, 6.17.

**Nitration of 6a: 3-Nitropyrrolo[2,1-*b*][1,3]benzothiazin-9-one (6e) and 1-Nitropyrrolo[2,1-*b*][1,3]benzothiazin-9-one (6f).** To a stirred solution of **6a** (0.75 g, 3.7 mmol) in acetic anhydride (40 mL) at 0 °C was added a solution of $Cu(NO_3)_2 \cdot 3H_2O$ (1.03 g, 4.25 mmol, 1.15 equiv) in acetic anhydride (60 mL) dropwise over 10 min. After stirring for 2.5 h on an ice bath, the dark mixture was poured slowly into 200 mL of a 5% $NaHCO_3$ solution and stirred for 30 min. The brown solid that formed was collected by vacuum filtration and dried overnight. The brown solid (0.70 g) was extracted for 3 h with $CHCl_3$ in a Soxhlet extractor and the obtained extract was concentrated to about 5 mL in vacuo and chromatographed (1:1 $CHCl_3$/hexanes). Four bands were obtained: the first (highest $R_f$) was starting material **6a**, 0.09 g. The next band (0.01 g) contained only the 3-isomer **6e**. The third band (0.04 g) contained a mixture of **6e** and **6f**, while the fourth (0.53 g) contained **6e**, **6f**, and impurities. Preparative TLC (1:1 $CHCl_3$/hexanes) was performed on the fourth band but only the 3-nitro isomer was isolated (trace amount).

**3-Nitropyrrolo[2,1-*b*][1,3]benzothiazin-9-one (6e):** $^1H$ NMR $\delta$ 8.62 (dd, $J$ = 1.51, 8.0 Hz, 1 H), 7.93 (d, $J$ = 3.84 Hz, 1 H), 7.78–7.46 (m, 3 H), 7.18 (d, $J$ = 3.84 Hz, 1 H).

**1-Nitropyrrolo[2,1-*b*][1,3]benzothiazin-9-one (6f)** (inferred from a mixture of the 1- and 3-isomers): $^1H$ NMR $\delta$ 8.48 (dd, $J$ = 1.33, 7.9 Hz, 1 H), 7.78–7.46 (m, 3 H), 7.42 (d, $J$ = 4.19 Hz, 1 H), 6.39 (d, $J$ = 4.19 Hz, 1 H).

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# Preparation and Remarkable Reactivity of the Elusive (1,1,3,3-Tetramethylallyl)lithium

Jose A. Cabral,[1a] Theodore Cohen,[1b] Wendel W. Doubleday,[1b] Ellen Francis Duchelle,[1a] Gideon Fraenkel,*[,1a] Bao Shan Guo,[1b] and Simon H. Yü[1a]

*Departments of Chemistry, The Ohio State University, Columbus, Ohio 43210, and University of Pittsburgh, Pittsburgh, Pennsylvania 15260*

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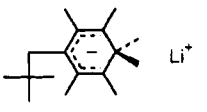
Although traditional methods of allyllithium production failed for (1,1,3,3-tetramethylallyl)lithium, it was readily prepared in a two-pot sequence starting with mesityl oxide. The key step is reductive lithiation of 4-(phenylthio)-2,4-dimethyl-2-pentene with lithium 1-(dimethylamino)naphthalenide. Treating the reductive lithiation product with trimethylstannyl chloride and the resulting allylstannane with methyllithium in the presence of *N,N,N,N*-tetramethylethylenediamine provided a solution of the allyllithium free of lithium thiophenoxide. This material adds to anthracene at −78 °C.

In our continuing investigations of structure and behavior of allyllithium–amine complexes, we developed a need for (1,1,3,3-tetramethylallyl)lithium, the simplest example of a highly alkylated conjugated carbanion salt. Most experimental evidence for carbanionic species in solution supports the conclusion that $\alpha$-alkyl substituents destabilize carbanions.[2] Whether such effects apply to peralkylated $\pi$-conjugated carbanions is less clear since there are relatively few examples of such species. Further, other interactions intrude. For example, the unexpected stability of the (peralkylcyclohexadienyl)lithium salt 1 was correctly ascribed to steric inhibition to aromatization.[3]

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In this paper, we reveal the difficulties encountered in the traditional methods of generating (1,1,3,3-tetramethylallyl)lithium, a highly efficient process for its preparation based on reductive lithiation of an allyl phenyl thioether, and an observation concerning its surprising reactivity towards anthracene.

## Results and Discussion

The traditional routes to allyllithiums such as ether cleavage[4] or metal reduction of the appropriate halide[5] do not result in (1,1,3,3-tetramethylallyl)lithium[6] and do not provide intermediates which could be used to prepare tin compounds, the best precursors of allyllithiums.[7] For

(1) (a) Ohio State University. (b) University of Pittsburgh.
(2) See, for example: Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum Press: New York, 1990; Vol. 2, pp 405–416.
(3) (a) Fraenkel, G.; Engelman, C.; Hallden-Abberton, M. P. *J. Org. Chem.* **1981**, *46*, 538. (b) Fraenkel, G.; Hallden-Abberton, M. P. *J. Am. Chem. Soc.* **1981**, *103*, 5657.
(4) (a) Eisch, J. J. *Organometal. Synth.* **1981**, *2*, 91. (b) Eisch, J. J.; Jacobs, A. M. *J. Org. Chem.* **1963**, *28*, 2145.
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(6) (a) Levina, R.; Egarova, S. *Obsch. Khim.* **1946**, *16*, 821. (b) Levina, R. *Ibid.* **1958**, *28*, 2049.

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