Allenic Compounds and Isothiocyanates as Key Building Units in the Synthesis of Heterocycles

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Abstract: Reaction between lithiated allenic compounds and isothiocyanates, R1N=C=S, in most cases gives exclusively thioimidates with the allenic structure, C=C=CC(SLi)=NR 1. These intermediates have been used in novel approaches to 2,3-dihydropyridines, pyrroles, quinolines, cyclobutanopyrrolines, and thiophene or dihydrothiophene derivatives. The procedures leading to the heterocycles with a nitrogen atom in the ring involve S-alkylation followed by simple heating or by treatment with copper(I) halide. 2-Aminothiophenes and 2-imino-2,5-dihydrothiophenes are formed by intramolecular nucleophilic attack of the thiolate moiety on the allenic system and subsequent addition of methyl iodide or protonation.

1 Introduction

Regioselective deprotonation using a strongly basic reagent is the first step in many syntheses involving allenic compounds. Reaction of the resulting intermediate with an electrophile in general affords a mixture of an allenic and an acetylenic derivative.1–3 The ratio of the products strongly depends upon the counter ion, the nature of the electrophile, and the substituents at positions close to the reacting centres. Also the polarity of the solvent may have a strong influence. Solutions of lithiated allenic ethers, H2C=C=CHR [R = OMe, t-BuO, OCH(Me)OEt, SMe], with BuLi at low temperatures in hexane–THF affords the lithium derivatives H2C=C=CHR (1, Scheme 1) regiospecifically. Analogous intermediates are readily generated under mild conditions from acetylenes MeC≡CR (R = alkyl, SMe or CH2NEt2).1–5 The γ-lithiation of mono-substituted allenic hydrocarbons, RCH=C=CHR, and geminally disubstituted allenes, R2C=C=CHR, with BuLi can be accomplished within the temperature range –50 to –10 °C. In the case of 1,2-butadiene, however, 10–15% α-lithiation has been observed.1,14

2 Generation of Allenic Lithium Compounds

Treatment of the allenic ethers and sulfur analogs, H2C=C=CHR [R = OMe, t-BuO, OCH(Me)OEt, SMe], with BuLi at low temperatures in hexane–THF affords the lithium derivatives H2C=C=CHR (1, Scheme 1) regiospecifically. Analogous intermediates are readily generated under mild conditions from acetylenes MeC≡CR (R = alkyl, SMe or CH2NEt2).1–5 The γ-lithiation of mono-substituted allenic hydrocarbons, RCH=C=CHR, and geminally disubstituted allenes, R2C=C=CHR, with BuLi can be accomplished within the temperature range –50 to –10 °C. In the case of 1,2-butadiene, however, 10–15% α-lithiation has been observed.1,14

3 Formation of 2,3-Dihydropyridines or Mixtures of 2,3-Dihydropyridines and Pyrroles

Reaction of intermediates 1 (Scheme 1) with alkyl isothiocyanates, methoxymethyl isothiocyanate, 2-vinyl-oxethyl isothiocyanate, or cyclohexyl isothiocyanate at temperatures below –70 °C as well as S-alkylation with alkyl iodides proceeds smoothly. Once temperatures higher than 25 °C are avoided during the work-up, the expected products 2 can be isolated in a fairly pure state.15 IR spectroscopy shows inter alia absorptions at ca. 1950 cm–1 (C=C=C) and ca. 1650 cm –1 (C=N). In the 1H NMR spectra the signals of the methylene group (H2C=C) are doubled, as are the other protons due to the presence of syn- and anti-isomers.

If the above-mentioned precautions during the work-up are not taken and bath temperatures during the isolation procedure are allowed to rise to 40 °C or higher, other products can be formed. In the case of R = OMe and R1 = R2 = H (1a, see Table 1) a mixture consisting of ca.70% of pyrrole 5a and ca. 30% of 2,3-dihydropyridine 4a is isolated in about 80% combined yield after distillation.15a The two components can be quantitatively
separated by treatment with dilute aqueous hydrochloric acid, followed by addition of potassium hydroxide to the acidic aqueous layer. Similar procedures using $\text{H}_2\text{C}=\text{CHOCH}_2\text{N}=\text{C}=\text{S}$, $\text{EtN}=\text{C}=\text{S}$, $\text{Me}_2\text{CHN}=\text{C}=\text{S}$, and $\text{c-C}_6\text{H}_11\text{N}=\text{C}=\text{S}$ lead to analogous results. In the last three cases, however, mainly the fully conjugated systems $3\text{b}$, $3\text{c}$, and $3\text{f}$, respectively, are isolated; in the case of $\text{MeOCH}_2\text{N}=\text{C}=\text{S}$ is the only isolated product; no trace of the intermediate $2\text{e}$ can be detected, even when the temperature is kept below room temperature during the work-up. Heating at elevated temperatures results in all cases in the formation of the cyclic products. Ratios of pyrrole $5\text{b}$–$5\text{d}$, $5\text{f}$ and dihydropyridine $4\text{b}$–$4\text{d}$, $4\text{f}$ (see Table 1) are different from that obtained in the reaction with methyl isothiocyanate. In the reactions with $\text{MeOCH}_2\text{N}=\text{C}=\text{S}$ dihydropyridines $4\text{e}$ are the exclusive end products. 

The formation of the 2,3-dihydropyridines may be visualized as a succession of a 1,5-hydrogen shift’s in 2, followed by electrocyclization of 3. We have been unable to elucidate the mechanism by which 2 are converted into the pyrroles 5. A possible route, involving protonation of the allenic ether system and subsequent cyclization, is shown in Scheme 1. Attempts to influence the ratio of 4 and 5 by treating 2 with protic acids or Lewis acids (such as lithium halides and zinc halides) failed (cf. the results mentioned in Section 3). If intermediate $2\text{a}$ is added drop-wise to hot (ca. 260 °C) paraffin oil, however, a ca. 60:40 mixture of 4a and 5a is obtained in a high yield. 

Dihydropyridines 4j–u are the only end products from the reaction of lithium compounds 1j–u and isothiocyanates.

Scheme 1

Reactions of the lithiated allenes 6 and 10 (Schemes 2 and 3) with isothiocyanates and subsequent S-methylation gives the rather stable compounds 7 and 8 or 11 and 12, respectively. For their conversion into the corresponding 2,3-dihydropyridines 9 and 13 heating at elevated temperatures is necessary. 

Elimination of methanol from 2,3-dihydropyridines 4e, n, and t, effected by heating or by treatment with catalytic amounts of hydrochloric acid, results in the formation of pyridines 14 in good yield. This method represents a novel approach to pyridines. The presence of an ethoxyethoxy group in 14j allows the easy transformation into 2-methylthio-3-pyridinol 15 (Scheme 4). 

The formation of pyridine 16 from the dihydropyridines 9a–c, which must proceed by elimination of hydrogen, methane, and methyl vinyl ether, respectively, is effected by refluxing under atmospheric pressure (Scheme 5).
3-Methoxy-1-methyl-2-(methylthio)pyrrole (5a) and 5-Methoxy-6-(methylthio)-2,3-dihydropyridine (4a) (Scheme 1)\textsuperscript{15}

a. Preparation of Methyl 2-Methoxy-N-methyl-2,3-butanedimidothioate (2a)

THF (65 mL) was added with cooling below 0 °C to a solution of BuLi (0.10 mol) in hexane (63 mL). Methoxyllene (8.4 g, 0.12 mol) was added at –80 °C over a few seconds, after which the temperature of the solution was allowed to rise to –40 °C. MeNCS (8.8 g, 0.12 mol) was added over 10 min as a solution in THF (10 mL), while keeping the temperature of the reaction mixture between –100 and –90 °C. After this addition, the temperature was allowed to rise gradually (over 15 min) to –40 °C. MeI (17.0 g, 0.20 mol, excess) was then added in one portion, after which the temperature of the yellowish suspension was allowed to rise to 10 °C. Ice water (100 mL) was added with vigorous stirring, after which the layers were separated and the aqueous layer extracted twice with small...
portions of Et₂O or pentane. The organic solution was dried over K₂CO₃.

b. Conversion of 2,3-Butadienimidothioate (2a) into Pyrrole 5a and 2,3-Dihydropyridine 4a

To the organic solution of 2,3-butadienimidothioate (2a) paraffin oil (40 ml) was added and the solvent was removed under water aspirator pressure. In the last stage of the evaporation procedure the temperature of the heating bath was increased to over 70 °C in order to initiate the cyclization. After removal of the last traces of solvent and the other volatile components under reduced pressure, the mixture of the product and paraffin oil was subjected to a distillation in vacuo, using a 20 cm Vigreux column. A ca. 7:3 mixture of the pyrrole 5a and 2,3-dihydropyridine 4a (bp 115–117 °C/15 Torr; nD²⁰ 1.5515) was collected in ca. 80% yield. After mixing the distillate with Et₂O–pentane obtained in 54% yield and 2,3-dihydropyridine 4a. Pyrrole 5a (bp 84–85 °C/2 Torr; nD²⁰ 1.5470) was obtained in 54% yield and 2,3-dihydropyridine 4a (bp 90–93 °C/2 Torr; nD²⁰ 1.5444) in 23% yield.

3-tert-Butyl)-6-(methylthio)-2,3-dihydropyridine (9a) (Scheme 2)²⁰,¹⁷

a. Preparation of Methyl N,5,5-Trimethyl-2,3-hexadienimidothioate (7a)

A solution of BuLi (0.11 mol) in hexane (69 mL) was mixed with THF (100 mL), while the temperature was kept below 0 °C. 4,4-Dimethyl-1,2-pentadiene (12.5 g, 0.13 mol) was added in one portion at –60 °C, after which the temperature was allowed to rise to –15 °C. The solution was stirred for an additional 15 min at –15 °C, then a mixture of MeNCS (7.3 g, 0.10 mol) and THF (10 mL) was added portionwise over 5 min at –100 °C. The temperature was allowed to rise to –40 °C, then MeI (21.3 g, 0.13 mol) was added. When the temperature of the light yellow suspension had reached 10 °C, water (100 mL) was added with vigorous stirring. The upper layer and two extracts (pentane) were dried over K₂CO₃, then the solvent was removed under reduced pressure. Distillation of the remaining liquid through a short Vigreux column afforded 2,3-hexadienimidothioate 7a (bp ca. 85 °C/0.7 Torr, nD²⁰ 1.528) in ca. 95% yield.

b. Ring Closure of 2,3-Hexadienimidothioate 7a with Formation of 2,3-Dihydropyridine 9a

The distillate 7a was heated under nitrogen to 215 °C, when an exothermic reaction started. Subsequent distillation in vacuum afforded 2,3-dihydropyridine 9a (bp 92 °C/2 Torr, nD²⁰ 1.5200) in 85% yield.

5-(tert-butyl)-2-(methylthio)pyridine (16, Scheme 5)²⁰,¹⁷

2,3-Dihydropyridine 9a (4.0 g) was heated under reflux and under inert gas for 30 min. Distillation gave pyridine 20 (by elimination of H₂; bp 78–80 °C/1 Torr, nD²⁰ 1.5464) in 75% yield.

4 Directed Synthesis of Pyrroles

As shown in the preceding section mixtures of pyrroles and 2,3-dihydropyridines or exclusively dihydropyridines resulted. Several attempts have been made to influence the cyclization of the intermediates 2 and 7 to favor formation of pyrroles, including treatment with catalytic amounts of protic or Lewis acids, organonickel or -palladium compounds, and copper(I) halides. Only the latter appear to effectively catalyze the cyclization of allene thioimidates to pyrroles. The formation of pyrroles from allene thioimidates 17 prepared from allene ethers [R = OMe or OCH(Me)OEt, Scheme 6] proceeds smoothly within the temperature range 10–30 °C.¹²,²⁰ The sulfur analogs (R = SMe) give only tar-like material. From azatrienes with a conjugated system of double bonds (3 or 8) no pyrroles are formed. The cyclization of allene compounds 17, R = alkyl (Scheme 6) to pyrroles proceeds sluggishly and results in low yields as the formation of fully conjugated azatrienes 3 (Scheme 1) is a thriving competing reaction. Successful results can be obtained with the intermediates 19 (Scheme 6), prepared from 4,4-dimethyl-1,2-pentadiene (6), though in the cases R¹ = aryl prolonged heating at 60–80 °C with a relatively large amount of copper halide is necessary. Reaction times may be shortened by using concentrated solutions of 19 in THF.¹²,²⁰

Competitive cyclization, resulting (after methylation) in the formation of 2-N,N-disubstituted aminothiophenes occurs in the reactions between lithiated methoxyallene and some aryl isothiocyanates. A few attempts have been made to avoid this reaction, but further research is necessary to optimize the pyrrole syntheses. It seems that pyrroles are the only or main products if the reaction between lithiated methoxyallene and aryl isothiocyanate is carried out with relatively large amounts of THF once the temperature of this reaction and that of the subsequent S-methylation, with a large excess of methyl iodide, is kept as low as possible. During reactions with methyl-substituted phenyl isothiocyanates, thiophene formation was not observed. The ring closure, which is assumed to take place in the absence of an external proton donor, may be explained as shown in Section 7, Scheme 9.¹²,²⁰ The very weakly basic 2-aminothiophene derivatives can be removed from the mixtures by repeated extraction with concentrated aqueous hydrochloric acid.¹²,²⁰
Pyrrole 18p having an OCH(Me)OEt group in the 3-position readily converts into 3-hydroxypyrrole 21, in equilibrium with very small amounts (5–10%) of the keto tautomer (Scheme 6). 21 3-Hydroxypyrroles and their keto-enol tautomerism have been described in detail. 22 The hydroxy form is favored in polar solvents where a hydrogen bond can form (e.g. DMSO) whereas the keto form is favored in non-polar solvents (e.g. CDCl₃), or in polar, protic solvents such as H₂O and MeOH. For derivatives having an ester group at the 2-position only the enol form is detected in CDCl₃. 22

Scheme 6

Pyrrrole 18p having an OCH(Me)OEt group in the 3-position readily converts into 3-hydroxypyrrole 21, in equilibrium with very small amounts (5–10%) of the keto tautomer (Scheme 6). 21 3-Hydroxypyrroles and their keto-enol tautomerism have been described in detail. 22 The hydroxy form is favored in polar solvents where a hydrogen bond can form (e.g. DMSO) whereas the keto form is favored in non-polar solvents (e.g. CDCl₃), or in polar, protic solvents such as H₂O and MeOH. For derivatives having an ester group at the 2-position only the enol form is detected in CDCl₃. 22

3-Hydroxy-1-methyl-2-(methylthio)pyrrole (21, Scheme 6)a 21

1-Methyl-3-(1-ethoxyethoxy)-2-(methylthio)pyrrole [18p, R = OCH(Me)OEt, R¹ = Me]

Ethoxyethyllallene (15.36 g, 0.12 mol) was added over a few seconds to a solution of BuLi (0.10 mol) in hexane (63 mL) and THF (75 mL), cooled at –90 °C. After stirring for 10 min at –70 °C, the solution was cooled to –100 °C and a mixture of MeNCS (7.3 g, 0.10 mol) and THF (20 mL) was added over a few minutes. After stirring for 15 min at –65 °C, Mel (21.6 g, 0.15 mol) was added, then the temperature was allowed to rise to 10 °C, and then finely powdered CuBr (1.3 g) was added with efficient stirring. The temperature of the reaction mixture rose by 10 °C or more over a period of 30 min. The reaction was completed by heating for an additional 30 min at ca. 50 °C, then a solution of NH₄Cl (15 g) and KCN (6 g) in water (100 mL) was added at r.t. with vigorous stirring. After ca. 10 min the layers were separated and the aqueous layer extracted with Et₂O. The organic solution was dried over K₂CO₃ and subsequently concentrated under reduced pressure. Traces of copper compounds were removed by flash chromatography on Al₂O₃ using Et₂O as eluent. After addition of Et₂NH (1 mL), the eluate was concentrated under reduced pressure and the remaining liquid distilled [the amine serves to neutralize traces of acid which might adhere to the glass and which may cause decomposition of the product containing the acid-sensitive OCH(Me)OEt group]. The pyrrole 18p [R = OCH(Me)OEt, R¹ = Me; bp ca. 115 °C/0.7 Torr, nD 23 1.5154, purity ca. 100%, GC], was obtained in 75% yield.

b. Conversion of 18p into 1-Methyl-2-methylthio-3-pyrrolol (21)

One drop of 30% aq HCl was added to a solution of 18p (4.3 g, 0.02 mol) in MeOH (20 mL) cooled to –5 °C. Initially the temperature was allowed to rise to 20 °C, then the mixture was heated for 5 min at 55 °C. The solution was then concentrated under reduced pressure and a solution of of KOH (0.5 g) in water (50 mL) was added. Extraction with Et₂O, followed by drying over MgSO₄ and concentration under reduced pressure gave pure pyrrolol 21 (bp ca. 100 °C/1 Torr, nD 20 1.5848, in 75% yield. The IR spectrum showed inter alia absorptions at 1539 (C=C) and 3341 cm⁻¹ (OH). The NMR spectrum of the CDCl₃ solution showed the presence of ca. 10% of the keto tautomer of 21 (in CCl₄ ca. 5% was present), while in the IR spectrum absorptions of the C=O group at 1639 and the C=C double bond at 1572 cm⁻¹ were visible.

Analogs of 21 with R¹ = Et, c-Hex, or Ph were obtained in a similar way from pyrroles 18q–s as undistilled products.

3-Methoxy-2-methylthio-1-phenylpyrrole (18g, Scheme 6a) 14,20

To a solution of BuLi (0.06 mol) in hexane (37 mL) and THF (30 mL), methoxyallene (5.6 g, 0.08 mol) was added at –90 °C and the solution was stirred for 15 min at ca. –70 °C, then a mixture of PhNCS (7 g, 0.052 mol) and THF (20 mL) was added dropwise over ca. 5 min at –90 to –80 °C. The red suspension was stirred for 15 min at ca. –60 °C, then Mel (14 g, 0.10 mol) was added at ca. –75 °C. After an additional 15 min the temperature was allowed to rise to 5 °C, then finely powdered CuI (0.7 g) was added. After stirring for 30 min at r.t., the mixture was heated to 50 °C, then the work-up as described in the preceding procedure was carried out and 18g [bp ca. 140°C/ca. 1 Torr; nD 20 1.6116; purity ca. 100% (GC)] was obtained in 52% yield (5.7 g).
1-(4-Fluorophenyl)-3-methoxy-2-(methylthio)pyrrole (18o, Scheme 6a)\textsuperscript{14,20}  
To a solution of lithiated methoxyallene \([\text{from } \text{BuLi (0.06 mol) in hexane (38 mL), THF (100 mL) and methoxyallene (5.5 g, 0.08 mol)}]\) was added 4-fluorophenyl isothiocyanate (7.7 g, 0.05 mol) at ca. \(-100 \degree C\), after which the temperature was allowed to rise to \(-60 \degree C\) over a period of 30 min. After stirring for an additional 20 min at ca. \(-65 \degree C\), MeI (40 g, 0.28 mol, large excess) was added at \(-60 \degree C\). The reaction mixture was stirred for an additional 15 min at ca. \(-70 \degree C\), then the cooling bath was removed and the temperature was allowed to rise to \(10 \degree C\). Finely powdered CuBr (1 g) was introduced with vigorous stirring. After stirring for 30 min at r.t., the mixture was heated for 10 min at 50 \degree C. After addition of an aqueous solution of NH\textsubscript{4}Cl and KCN (cf. preceding experiments), the product, (bp ca. 120 \degree C/0.3 Torr) was isolated in 69\% yield. Upon standing at r.t. yellow crystals formed.

2-tert-Butyl-5-methylthio-1-phenylpyrrole (20d, \(R_1 = \text{Ph}, \text{Scheme 6b}\))\textsuperscript{14,20}  
To a solution of BuLi (0.07 mol) in THF (45 mL) and hexane (45 mL) was added at \(-50 \degree C\) 4,4-dimethyl-1,2-pentadiene (10 g, 0.10 mol). After stirring for an additional 20 min at \(-15 \degree C\), the solution was cooled to \(-100 \degree C\) and a solution of PhNCS (6.75 g, 0.05 mol) in THF (20 mL) was added over a few seconds while keeping the temperature of the reaction mixture below \(-80 \degree C\). After an additional 10 min (at \(-85 \degree C\)), Mel (12 g, 0.08 mol) was added, and the temperature was allowed to rise to \(10 \degree C\). A solution of CuBr (5 g) and anhydrous LiBr (6 g) in THF (25 mL) was added and the reaction mixture was heated under reflux for 4 h. After cooling to r.t., a solution of NH\textsubscript{4}Cl (15 g) and KCN (10 g) in water (100 mL) was added with vigorous stirring. The aqueous phase was separated and extracted 3 times with \(\text{Et}_2\text{O}\). The organic layer and ethereal extracts were concentrated under reduced pressure and the remaining liquid subjected to flash chromatography on \(\text{Al}_2\text{O}_3\) in order to remove traces of copper compounds. The (ethereal) eluate was concentrated under reduced pressure and the remaining liquid distilled through a short column. Pyrrole derivative 20d, (bp ca. 110 \degree C/0.7 Torr, \(n_D^{20} 1.5773\)) was obtained in 75\% yield.

5 Synthesis of Quinolines

The formation of 4-methyl-2-(methylthio)quinoline by thermal rearrangement of the thioimidate obtained from the reaction of allenylmagnesium bromide with phenyl isothiocyanate and subsequent S-methylation was reported in a short communication.\textsuperscript{23a} A similar sequence with \(\text{Me}_2\text{C}=\text{C}=\text{CHLi, PhN}=\text{C}=\text{S, and Mel (Scheme 7)}\) afforded 4-isoproplylpropyl-2-(methylthio)quinoline (25b).\textsuperscript{23a} Azapolyenic systems, as precursors of quinoline rings, can be constructed by reaction of allenylmagnesium bromide with N-arylsubstituted chloroformamidines.\textsuperscript{23b} A few electrocyclizations of all-carbon systems \(\text{C} = \text{C} = \text{C} = \text{C} = \text{C} = \text{C}\), analogous to 23\textsuperscript{23} in Scheme 7 have been reported.\textsuperscript{23c}

Using 4,4-dimethyl-1,2-pentadiene, \(t\)-Bu\textsubscript{2}CH=CH=CH\textsubscript{2}, or geminally disubstituted allenes, \(R_2\text{C}=\text{C}=\text{CH}_2\), and phenyl or substituted-aryl isothiocyanates a number of quinoline derivatives can be prepared with good yields.\textsuperscript{14,18,20,23d} Syntheses with 2-substituted phenyl isothiocyanates gives 8-substituted quinolines, while the 6-substituted derivatives are obtained when using 4-substituted phenyl isothiocyanates. Reactions with 3-substituted phenyl isothiocyanates in principle may afford both 5- and 7-substituted quinolines. 7-Trifluoromethylquinoline is obtained as the predominant product from the synthesis starting with 3-CF\textsubscript{3}C\textsubscript{6}H\textsubscript{4}N=C=S and 4,4-dimethyl-1,2-pentadiene.\textsuperscript{14,20}

Scheme 7

The synthesis with methoxyallene, MeOCH=CH=CH\textsubscript{2}, and PhN=C=S gives a mixture of approximately equal amounts of 4-methyl-3-methoxy-2-(methylthio)quinoline and 1-phenyl-3-methoxy-2-(methylthio)pyrrole in approximately 60\% combined yield.\textsuperscript{25} The compounds can be separated by treatment of an ethereal solution of the mixture with dilute hydrochloric acid and subsequent neutralization of the aqueous layer with potassium hydroxide. Using methylthioallene results in 2,3-bis(methylthio)quinoline being obtained as the only product in a fair yield.\textsuperscript{25}

2-Methylthio-4-neopentylquinoline (25a, Scheme 7)\textsuperscript{24c}  
4,4-Dimethyl-1,2-pentadiene, (11.5 g, 0.12 mol) was added in one portion to a solution of BuLi (0.10 mol) in hexane (63 mL) and THF (70 mL) cooled to \(-50 \degree C\). After the addition the temperature was allowed to rise to \(-15 \degree C\), and maintained at this temperature for 30 min. The almost clear solution was cooled to \(-100 \degree C\), a mixture of PhNCS (13.5 g, 0.10 mol) and THF (20 mL) was added over 10 min, while keeping the temperature of the reaction mix-
ture below −80 °C. After an additional 15 min, MeI (20 g, 0.14 mol) was added at −80 °C and the cooling bath was removed. Once the temperature reached 5 °C, water (60 mL) was added and the solution was then extracted with Et₂O. After drying over MgSO₄, the organic solution was concentrated under reduced pressure (bath temperature < 40 °C) to give 5,5-dimethyl-\( N \)-phenyl-2,3-hexadienimidothioate (23a) in quantitative yield. The crude azatriene 23a was mixed with toluene (30 mL) and the solution heated at ca. 100 °C under a reflux condenser. A strongly exothermic reaction ensued. After the reflux has subsided the solution was heated under reflux for an additional 10 min. Removal of the toluene under reduced pressure followed by distillation gave quinoline 25a, (bp ca. 135 °C/0.5 Torr, \( n_D^{20} \) 1.6090) in 82% yield.

6 Synthesis of Cyclobutanopyrrolines

As shown in Scheme 3 the azatriene 12 obtained from the reaction between 3-methyl-1,2-butadienyllithium 10 and methyl or ethyl isothiocyanate gives dihydropyridine 13 upon strong heating. Using 3-methyl-1,2-butadienyllithium and \( i \)-propyl isothiocyanate (\( R_1 = R_2 = Me \)) the azatriene 28 (\( R = R_1 = R_2 = Me \)) is obtained by a similar sequence (Scheme 8). This compound is stable at temperatures of at least 190 °C, but heating at about 220 °C under normal pressure (reflux) surprisingly does not afford the dihydropyridine 29, but cyclobutanopyrrole 30 as the only product in excellent overall yield. The analogs 31, 32, and 33 are obtained with good overall yields from syntheses with geminally disubstituted allenyllithiums and isopropyl or cycloalkyl isothiocyanates. The advantage of this route over electrocyclization, for the formation of 2,3-dihydropyridines, is that steric repulsion is avoided. Explanations for the formation of cyclobutanopyrrolines remain speculative, as attempts to detect intermediates from the cyclizations of 28 have been unsuccessful.

Cyclobutanopyrrolines 31–33 were prepared by heating the precursors 28 under an inert gas at approximately 230 °C. The progress of the cyclization was followed by \( ^1H \) NMR spectroscopy, after disappearance of the CH= signals the product was isolated by vacuum distillation. If compound 28 (\( R = Me, R_1R_2C = (CH_2)_5C \)) was heated at approximately 280 °C for 10–15 minutes, appreciable amounts of 1-cyclohexyl-5-methyl-2(1H) pyridinethione (up to about 25% yield) could be isolated as a by-product by crystallization. Its formation may be explained by assuming a 1,7-hydrogen shift in the azatriene \( Me_2C=C(CH_2)_5C(SMe)=N=Me(C)CMe=CH(NMe)=C(SMe)=Me(C)CMe=C(SMe)=N=Me(C)CMe=CHMe \).27

Scheme 8
reduced pressure to afford 8.51 g (93% yield) of azatriene 27 as a light mobile liquid.

b. 4-Methyl-N-(1-Methylethylidene)-1-methylthio-1,3-pentadien-1-amine (28, R = R1 = R2 = Me)

Heating of 27 for a few minutes at ca. 100 °C, followed by distillation, gave 28 (bp ca. 85 °C/0.7 Torr, n_D^20 1.5610) in 90% yield.

c. 1,6,6-Trimethyl-3-methylthio-2-azabicyclo[3.2.0]hept-2-ene (30)

Azatriene 28 (R = R1 = R2 = Me) was heated in an atmosphere of inert gas under reflux for 15 min (internal temperature ca. 220 °C). After this period the refractive index had reached its minimal value. The product 30 (bp 215 °C/760 Torr, n_D^20 1.5060) was isolated in 87% yield by distillation through a very short column.

Cyclobutanopyrrolines 31–33 were prepared by heating the precursors 28 under inert gas at ca. 230 °C. The progress of the cyclization was followed by 1H NMR spectroscopy. After disappearance of the CH= signals the product was isolated by vacuum distillation. If compound 28 with R = Me and R1R2C = (CH2)5C was heated at ca. 280 °C for 10–15 min, appreciable amounts of 1-cyclohexyl-5-methyl-2(1H) pyridinethione (up to ca. 25% yield) could be isolated as a by-product by crystallization. Its formation may be explained by assuming a 1,7-hydrogen shift in the azatriene Me2C=CHCH=C(SMe)N=C(CH2)5 affording H2C=C(Me)CH=CHC(SMe)=N=C-hex, electrocyclization of the latter to the 1,2-dihydropyridine and elimination of methane.

7 Synthesis of Thiophene and Dihydrothiophene Derivatives

Adducts 34 obtained from intermediate 1 (Scheme 9) suggests the possibility of ring closure leading ultimately to formation of thiophene derivatives. This expectation was realized with successful one-pot procedures for several 3-substituted 2-aminothiophenes 38 and 39. As shown in Scheme 9 the initial cyclization product 35 has to be transformed into the amide 36 → 37 by a proton-metal (charge) exchange. In Section 4 we have seen that during reactions between lithiomethoxyallene and a number of substituted-phenyl isothiocyanates this cyclization can proceed to a considerable extent at low temperatures in the absence of a proton-donating agent. It can be completed by stirring

<table>
<thead>
<tr>
<th>Methoda</th>
<th>R</th>
<th>R1</th>
<th>Yield (%)b</th>
<th>Methoda</th>
<th>R</th>
<th>R1</th>
<th>Yield (%)b</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>MeO</td>
<td>Me</td>
<td>32</td>
<td>E</td>
<td>MeO</td>
<td>2-FPh</td>
<td>66</td>
</tr>
<tr>
<td>B</td>
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<td>Me</td>
<td>61</td>
<td>E</td>
<td>MeO</td>
<td>2-CIPh</td>
<td>67</td>
</tr>
<tr>
<td>E</td>
<td>MeO</td>
<td>Me</td>
<td>75</td>
<td>E</td>
<td>MeO</td>
<td>2-BrPh</td>
<td>69</td>
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<tr>
<td>E</td>
<td>MeS</td>
<td>Me</td>
<td>67</td>
<td>C</td>
<td>MeO</td>
<td>3-CIPh</td>
<td>70</td>
</tr>
<tr>
<td>C</td>
<td>MeO</td>
<td>Et</td>
<td>70</td>
<td>E</td>
<td>MeO</td>
<td>3-CIPh</td>
<td>79</td>
</tr>
<tr>
<td>A</td>
<td>MeO</td>
<td>Ph</td>
<td>70</td>
<td>E</td>
<td>MeO</td>
<td>4-FPh</td>
<td>76</td>
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<tr>
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<td>MeO</td>
<td>3-MePh</td>
<td>41</td>
<td>E</td>
<td>MeO</td>
<td>4-CIPh</td>
<td>63</td>
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<tr>
<td>A</td>
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<td>4-MePh</td>
<td>46</td>
<td>A</td>
<td>MeO</td>
<td>3,4-Cl2Ph</td>
<td>76</td>
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<tr>
<td>A</td>
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<td>2,6-Me2Ph</td>
<td>73c</td>
<td>C</td>
<td>Me</td>
<td>Me</td>
<td>61</td>
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<tr>
<td>A</td>
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<td>3-F3CPh</td>
<td>71</td>
<td>D</td>
<td>Me</td>
<td>Me</td>
<td>42</td>
</tr>
<tr>
<td>E</td>
<td>MeO</td>
<td>4-F2CPh</td>
<td>68</td>
<td>D</td>
<td>Et</td>
<td>Me</td>
<td>60</td>
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<tr>
<td>E</td>
<td>MeO</td>
<td>4-Me2NPh</td>
<td>31</td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

* A: A solution of 34 was heated for 30 min at 40 °C, then MeI was added at 0 °C, followed by heating at 40 °C. B: To a solution of 34 (0.05 molar scale) was added at –40 °C powderd r-BuOK (1 equiv). After heating for 45 min at ca. 35–45 °C, MeI was added at –15 °C, followed by heating. C: To a solution of 34 (0.05 molar scale) was added at –50 °C a solution of r-BuOK (1 equiv) in THF (20 mL). After heating for 30 min at 40 °C, MeI was added at 0 °C, followed by heating. D: To a solution of 34 (0.05–0.10 molar scale) was added of r-BuOK (1 equiv) in THF (40 mL), followed by heating to 10–15 °C, addition of DMSO (30 mL), heating for 20–40 min at ca. 40 °C, addition of some excess of MeI or Me2SO4 at 0–5 °C and stirring at r.t. E: To a solution of 34 (0.05 molar scale) were successively added at –50 °C r-BuOH (1 equiv) in THF and r-BuOK (1 equiv) in DMSO (30 mL). After 30 min at 25 °C excess MeI was added at 0 °C, followed by heating.

* Not optimized.

* N-(2,6-Dimethylphenyl)-N-(3-methoxy-5-methyl-2(SH)-thiophenyliden)amine was obtained instead of the expected N-(2,6-dimethylphenyl)-3-methoxy-N-methyl-2-thiophenamine.
the reaction mixture for a limited period at temperatures
above 0 °C. Subsequent addition of water or methyl io-
dide affords the aminothiophenes 38 or 39, respectiv-
ely.20,28,29 Yields are high in the cases of R 1 = Ph, 3,4-
Cl2C6H4 and 3-F3CC6H4 and moderate if R 1 =3 - MeC6H4
and 4-MeC6H4 (method A). In variants B–E of Table 2 a
solution of 34 is treated with t-BuOK prior to carrying out
the final methylation (cf. note a of this table), thus creating
more strongly nucleophilic conditions for the ring closure
of 34.

\[
\begin{align*}
38 & \quad 39 \\
& \quad \text{R = OMe; R1 = Alkyl, Ph, 2-, 3-, 4-subst.-Ph} \\
& \quad \text{R = Alkyl; R1 = alkyl} \\
& \quad \text{R = SMe; R1 = Me, Ph}
\end{align*}
\]

Scheme 9

\[
\begin{align*}
R & = \text{Me or Aryl} \\
R' & = \text{Me or Aryl}
\end{align*}
\]

Scheme 10

3-Methoxy-N-phenyl-2-thiophenamine (38, Schemes 9 and 10)29

The reaction mixture obtained by the addition of phenyl
isothiocyanate to lithiomethoxyallene (cf. preceding pro-
cedure) was allowed to reach 0 °C, then water (100 mL)
was added followed by stirring for 15 min at r.t. The ami-
nothiophene was isolated as described in the preceding
procedure (bp ca. 140 °C/0.6 Torr, n\textsubscript{D} 20 1.6333) in 79%
yield.

In analogy with the reactions in Scheme 9 the ami-
nothiophenes 41 or 42 and iminodihydrothiophenes 43
can be obtained in excellent yields from 4,4-dimethyl-1,2-
pentadienyllithium (6) and geminally disubstituted allenyllithiums 26, respectively (Schemes 11 and 12).31,32

\[
\begin{align*}
41 & \quad 42 \\
& \quad \text{R1 = alkyl or aryl}
\end{align*}
\]

Scheme 11

\[
\begin{align*}
43 & \quad 26 \\
& \quad \text{R = alkyl or R2C = (CH}_2\text{)C; R1 = alkyl or aryl}
\end{align*}
\]

Scheme 12

8 Concluding Remarks

Many reactions between lithiated allenic compounds and
electrophiles afford a mixture of the allenic and acetylenic
derivative.1–3 Synthetically useful selectivities of func-
tionalizations may be attained by replacing lithium by oth-
er metals, such as zinc, titanium, and aluminium.33–36
Remarkably, reactions of lithiated allenes with isothiocya-
ates in most cases afford allenic thioimidates with very
high selectivities, making these metal-metal exchanges,

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for which stoichiometric amounts of halides or other derivatives of these metals are required, unnecessary. The ready access to these allenic thiiumidates allows a convenient approach to the heterocyclic systems mentioned in the preceding sections. The 2,3-dihydropropyrindines are scarcely studied. Some of the dihydropropyrindines obtained in our investigations can be converted with good yields into derivatives of pyridine that are not accessible otherwise. Cyclobutanopyrrolines represent a new class of compounds. Syntheses using methoxyllene or other allenic ethers $\text{H}_2\text{C}==\text{C}=\text{CHOR}$ afford heterocyclic compounds containing the OR substituent. The OCH(Me)OEt substituent, which is introduced when using the readily available $\text{H}_2\text{C}==\text{C}=\text{CHOCH(Me)OEt}$, can be easily transformed into the hydroxyl function under mildly acidic conditions.

Although isocyanates seem less versatile ‘partners’ for metallated allenes than their thio analogs (isothiocyanates), our preliminary investigations suggest that they can be also successfully used in the synthesis of heteroatomic open-chain and cyclic compounds. Thus, reactions of lithiated allenes with alkyl or aryl isocyanates give easy open-chain and cyclic compounds. Thus, reactions of lithiated allenes with alkyl or aryl isocyanates give easy formations into the hydroxyl function under mildly acidic conditions.

Several acetylenic compounds from which allenic carbanions can be generated have been incorporated in the reactions with isothiocyanates, leading to new families of functionality pyrolyles, dihydropropyrindines, quinolines, thiophenes, cyclobutenes, etc.20,46

References

(14) Unpublished results from the author’s laboratory.


