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, $R^1N=C=S$, 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.

Key words: thioimidates, azatrienes, 2,3-dihydropyridines, pyrroles, quuinolines, cyclobutanopyrrolines, 2-aminothiophenes, 2-imino-2,5-dihydrothiophenes

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, $H_2C=C=C(Li)OR$, in organic solvents give only the allenic derivatives in reactions with a wide variety of electrophiles. Several useful applications of allenic ethers in syntheses of heterocyclic compounds have been reported.[4–12]

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Our research dealing with reactions between metallated acetylenes or allenes[13] and thiocarbonyl compounds was extended in 1995 to include reactions involving heterocumulenes, in particular isothiocyanates.

2 Generation of Allenic Lithium Compounds

Treatment of the allenic ethers and sulfur analogs, $H_2C=C=CHR$ [R = OMe, *t*-BuO, OCH(Me)OEt, SMe], with BuLi at low temperatures in hexane–THF affords the lithium derivatives $H_2C=C=C(Li)R$ (**1**, Scheme 1) regiospecifically. Analogous intermediates are readily generated under mild conditions from acetylenes $MeC{\equiv}CR$ (R = alkyl, SMe or CH_2NEt_2).[1–5] The γ-lithiation of mono-substituted allenic hydrocarbons, $RCH=C=CH_2$, and geminally disubstituted allenes, $R_2C=C=CH_2$, 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 Dihydropyridines and Pyrroles

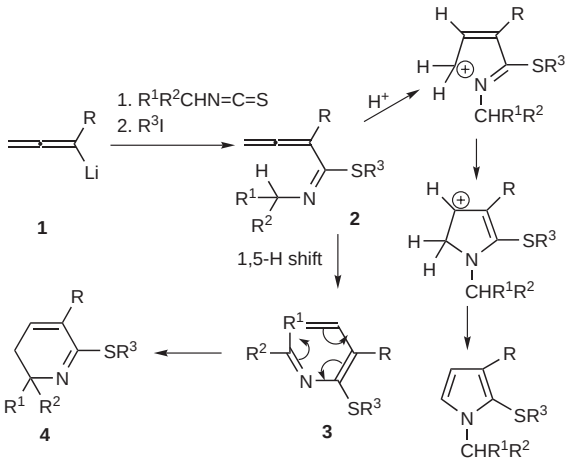
Reaction of intermediates **1** (Scheme 1) with alkyl isothiocyanates, methoxymethyl isothiocyanate, 2-vinyloxyethyl isothiocyanate, or cyclohexyl isothiocyanate at temperatures below –70 °C as well as S-alkylation with alkyl iodides proceeds smoothly. Once temperatures higher than 25 °C are avoided 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 (C=N) cm^{-1}. In the ^1H NMR spectra the signals of the methylene group ($H_2C=C$) 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 $R^1 = R^2 = H$ (**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 $H_2C{=}CHOCH_2CH_2N{=}C{=}S$,[15c] $EtN{=}C{=}S$, $Me_2CHN{=}C{=}S$, and *c*-$C_6H_{11}N{=}C{=}S$[15b] lead to analogous results. In the last three cases, however, mainly the fully conjugated systems **3b**, **c**, and **f**, respectively, are isolated; in the case of $MeOCH_2N{=}C{=}S$ **3e** is the only isolated product; no trace of the intermediate **2e** can be detected, even when the temperature is kept below room temperature during the work-up.[16a] Heating at elevated temperatures results in all cases in the formation of the cyclic products. Ratios of pyrrole **5b**–**d**, **f** and dihydropyridine **4b**–**d**, **f** (see Table 1) are different from that obtained in the reaction with methyl isothiocyanate. In the reactions with $MeOCH_2N{=}C{=}S$ dihydropyridines **4e** are the exclusive end products.[16]

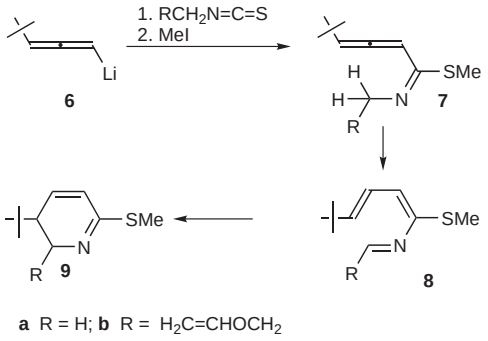
The formation of the 2,3-dihydropyridines may be visualized as a succession of a 1,5-hydrogen shift's in **2**, followed by electrocyclization of **3**. We have been unable to elucidate the mechanism by which **2** are converted into the pyrroles **5**. A possible route, involving protonation of the 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 **2a** is added dropwise to hot (ca. 260 °C) paraffin oil, however, a ca. 60:40 mixture of **4a** and **5a** is obtained in a high yield.[14]

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



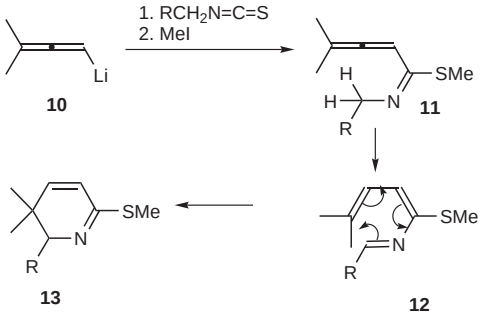
Scheme 1

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.[15f,17,18]



a R = H; **b** R = $H_2C{=}CHOCH_2$

Scheme 2

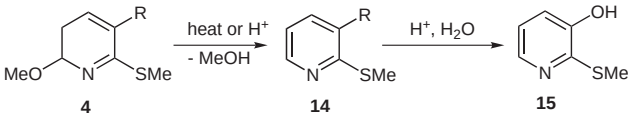


a R = H; **b** R = Me

Scheme 3

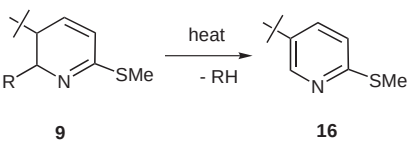
Elimination of methanol from 2,3-dihydropyridines **4e**, **n**, and **t**, effected by heating or by treatment with catalytic amounts of hydrochloric acid, results in the formation of pyridines **14** in good yield. This method represents a novel approach to pyridines.[16] The presence of an ethoxyethoxy group in **14j** allows the easy transformation into 2-methylthio-3-pyridinol **15** (Scheme 4).[16b]

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).[14,17]



e R = OMe
j R = OCH(Me)OEt
n R = SMe
t R = Me

Scheme 4



a R = H
b R = Me
c R = $CH_2OCH{=}CH_2$

Scheme 5

Table 1 Formation of 2,3-Dihydropyridines **4** or Mixtures of **4** and Pyrroles **5** (Scheme 1)

	R	R^1	R^2	R^3	Yields[a] of end products (%)	
					4	**5**
a	OMe	H	H	Me	23	54
b	OMe	H	Me	Me	53	15
c	OMe	Me	Me	Me	42	18
d	OMe	H	H_2C=CHOCH$_2$	Me	34	33
e	OMe	H	OMe	Me	73	–
f	OMe	–C=(CH$_2$)$_5$C–		Et	63[b]	11[b]
g	*t*-BuO	H	H	Me	[c]	[c]
h	*t*-BuO	H	H	Et	11[d]	85[d]
i	OCH(Me)OEt	H	Me	Me	[e]	[e]
j	OCH(Me)OEt	H	OMe	Me	84	–
k	SMe[f]	H	H	Me	65	–
l	SMe[f]	Me	Me	Me	70	–
m	SMe[f]	H	H_2C=CHOCH$_2$	Me	57	–
n	SMe[f]	H	OMe	Me	100[b]	–
o	Me[g]	H	H	Me	92	–
p	Me[g]	H	Me	Me	80[b]	–
q	Me[g]	Me	Me	Me	85	–
r	Me[g]	H	H_2C=CHOCH$_2$	Me	68	–
s	Me[g]	R^1R^2C=(CH$_2$)$_5$C	Me	75	–	
t	Me[g]	H	OMe	Me	100[b]	–
u	CH_2NEt_2[h]	H	H	Me	68	–

[a] Isolated yields are based on the reagent used in the lowest molar amounts, mostly BuLi; satisfactory microanalyses were obtained.
[b] Undistilled.
[c] Qualitative experiment; no yields determined; excellent NMR spectra and satisfactory microanalyses for **4** and **5**.
[d] Combined yield > 80%; the ratio **5**/**4**, determined with GC, was about 8:1.
[e] Ratio of **4**/**5** was about 6:1 (GC); no yields determined; attempts to separate the components via treatment with HCl–H_2O, **4** was converted into 6-methyl-2-methylthio-5,6-dihydro-3(4*H*) pyridinone, which was isolated in about 30% yield.
[f] A mixture of MeSCH=C=CH$_2$ and MeSC≡CMe was used.
[g] The lithiated allenic compound **1** was generated from MeC≡CMe and BuLi.
[h] The lithiated allenic compound **1** was generated by treating MeC≡CCH$_2$NEt$_2$ with a 1:1 mixture of BuLi and *t*-BuOK at temperatures below –80 °C and subsequently adding anhydrous LiBr.

3-Methoxy-1-methyl-2-(methylthio)pyrrole (5a) and 5-Methoxy-6-(methylthio)-2,3-dihydropyridine (4a) (Scheme 1)[15]

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

THF (65 mL) was added with cooling below 0 °C to a solution of BuLi (0.10 mol) in hexane (63 mL). Methoxyallene (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 Et_2O or pentane. The organic solution was dried over K_2CO_3.

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; n_D^{20} 1.5515) was collected in ca. 80% yield. After mixing the distillate with Et_2O–pentane (1:1, 100 ml), the solution was vigorously shaken with a ca. 20% excess of a cold (0 °C) 1 M aqueous solution of HCl. The acidic aqueous layer was extracted twice with small portions of pentane, subsequently treated with KOH pellets (5 g), after which three extractions with Et_2O were carried out. Both organic solutions were dried over K_2CO_3. Concentration under reduced pressure followed by distillation afforded pyrrole **5a** and 2,3-dihydropyridine **4a**. Pyrrole **5a** (bp 84−85 °C/2 Torr; n_D^{20} 1.5470) was obtained in 54% yield and 2,3-dihydropyridine **4a** (bp 90−93 °C/2 Torr; n_D^{20} 1.5444) in 23% yield.

3-(*tert*-Butyl)-6-(methylthio)-2,3-dihydropyridine (9a) (Scheme 2)[15f,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, 0.15 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 K_2CO_3, 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, n_D^{20} 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, n_D^{20} 1.5200) in 85% yield.

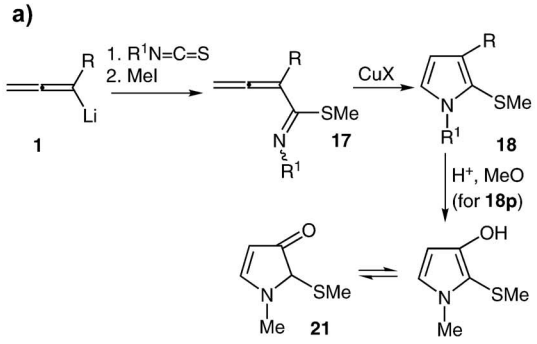
5-(*tert*-butyl)-2-(methylthio)pyridine (**16**, Scheme 5)[15f,17]

2,3-Dihydropyridine **9a** (4.0 g) was heated under reflux and under inert gas for 30 min. Distillation gave pyridine **2o** (by elimination of H_2; bp 78−80 °C/1 Torr, n_D^{20} 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 allenic thioimidates to pyrroles. The formation of pyrroles from allenic thioimidates **17** prepared from allenic ethers [R = OMe or OCH(Me)OEt, Scheme 6] proceeds smoothly within the temperature range 10–30 °C.[19,20] 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 allenic 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 R^1 = 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.[14,20]

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.[14,20] The very weakly basic 2-aminothiophene derivatives can be removed from the mixtures by repeated extraction with concentrated aqueous hydrochloric acid.[14,20]



R = OMe; R^1: **a** Me, **b** Et, **c** *i*-C_3H_7, **d** *c*-C_5H_9, **e** *c*-C_6H_{11}, **f** $H_2C{=}CHO(CH_2)_2$, **g** Ph, **h** 2-FC_6H_4, **i** 2-ClC_6H_4, **j** 2-$F_3CC_6H_4$, **k** 3-MeC_6H_4, **l** 3-$MeOC_6H_4$, **m** 2,6-$Me_2C_6H_4$, **n** 4-MeC_6H_4, **o** 4-FC_6H_4,

R = OCH(Me)OEt, R^1: **p** Me, **q** Et, **r** *c*-C_6H_{11}, **s** Ph

R^1: **a** Me, **b** Et, **c** $H_2C{=}CHO(CH_2)_2$, **d** Ph, **e** 2-MeC_6H_4, **f** 2-FC_6H_4, **g** $F_3CC_6H_4$, **h** 3-FlC_6H_4, **i** 3-ClC_6H_4, **j** 4-ClC_6H_4, **k** 4-BrC_6H_4, **l** 4-$F_3CC_6H_4$, **m** 4-$Me_2NC_6H_4$

Scheme 6

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. $CDCl_3$), or in polar, protic solvents such as H_2O and MeOH. For derivatives having an ester group at the 2-position only the enol form is detected in $CDCl_3$.[22]

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

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

Ethoxyethoxyallene (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, MeI (21.6 g, 0.15 mol) was added, 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 NH_4Cl (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 Et_2O. The organic solution was dried over K_2CO_3 and subsequently concentrated under reduced pressure. Traces of copper compounds were removed by flash chromatography on Al_2O_3 using Et_2O as eluent. After addition of Et_2NH (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, R^1 = Me; bp ca. 115 °C/0.7 Torr, n_D^{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 Et_2O, followed by drying over $MgSO_4$ and concentration under reduced pressure gave pure pyrrolol **21** (bp ca. 100 °C/1 Torr, n_D^{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 $CDCl_3$ solution showed the presence of ca. 10% of the keto tautomer of **21** (in CCl_4 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 R^1 = 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 (50 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 MeI (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; n_D^{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)[14,20]

To a solution of lithiated methoxyallene [from 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 °C, after which the temperature was allowed to rise to –60 °C over a period of 30 min. After stirring for an additional 20 min at ca. –65 °C, MeI (40 g, 0.28 mol, large excess) was added at –60 °C. The reaction mixture was stirred for an additional 15 min at ca. –70 °C, then the cooling bath was removed and the temperature was allowed to rise to 10 °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 °C. After addition of an aqueous solution of NH_4Cl and KCN (cf. preceding experiments), the product, (bp ca. 120 °C/0.3 Torr) was isolated in 69% yield. Upon standing at r.t. yellow crystals formed.

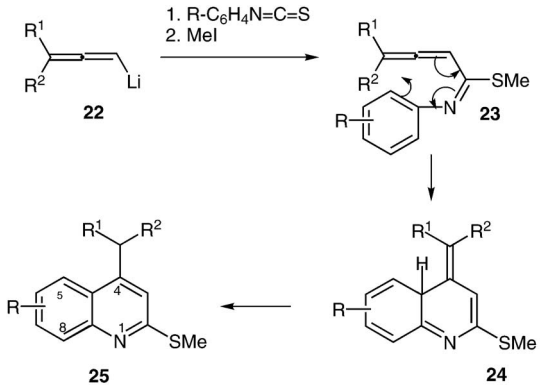
2-*tert*-Butyl-5-methylthio-1-phenylpyrrole (20d, R^1 = Ph, Scheme 6b)[14,20]

To a solution of BuLi (0.07 mol) in THF (45 mL) and hexane (45 mL) was added at –50 °C 4,4-dimethyl-1,2-pentadiene (10 g, 0.10 mol). After stirring for an additional 20 min at –15 °C, the solution was cooled to –100 °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 °C. After an additional 10 min (at –85 °C), MeI (12 g, 0.08 mol) was added, and the temperature was allowed to rise to 10 °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_4Cl (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 Et_2O.The organic layer and ethereal extracts were concentrated under reduced pressure and the remaining liquid subjected to flash chromatography on Al_2O_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 °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.[23a] A similar sequence with Me_2C=C=CHLi, PhN=C=S, and MeI (Scheme 7) afforded 4-isopropylpropyl-2-(methylthio)quinoline (**25b**).[23a] Azapolyenic systems, as precursors of quinoline rings, can be constructed by reaction of allenylmagnesium bromide with N-arylsubstituted chloroformamidines.[23b] A few electrocyclizations of all-carbon systems C=C=C–C=C–C=C, analogous to **23**→**24** in Scheme 7 have been reported.[23c]

Using 4,4-dimethyl-1,2-pentadiene, *t*-BuCH=C=CH_2, or geminally disubstituted allenes, R_2C=C=CH_2, [R = Me or $R_2C = (CH_2)_5C$] and phenyl or substituted-aryl isothiocyanates a number of quinoline derivatives can be prepared with good yields.[14,18,20,24] 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-$CF_3C_6H_4$N=C=S and 4,4-dimethyl-1,2-pentadiene.[14,20]



R = H: **a** R^1 = H, R^2 = *t*-Bu; **b** R^1 = R^2 = Me; **c** R^1R^2C = *c*-Hexyl
R = 2-FPh, 2-MePh, 2-CF_3Ph, 3-FPh, 3-ClPh, 3-CF_3Ph, 3-MeOPh, 4-FPh, 4-ClPh, 4-BrPh, 4-CF_3Ph, 4-Me_2NPh; R^1 = H, R^2 = *t*-Bu

Scheme 7

The synthesis with methoxyallene, MeOCH=C=CH_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.[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.[25]

2-Methylthio-4-neopentylquinoline (25a, Scheme 7)[24c]

4,4-Dimethyl-1,2-pentadiene, (11.5 g, 0.12 mol) was added in one portion to a solution of of BuLi (0.10 mol) in hexane (63 mL) and THF (70 mL) cooled to –50 °C. After the addition the temperature was allowed to rise to –15 °C, and maintained at this temperature for 30 min. The almost clear solution was cooled to –100 °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 Et_2O. After drying over $MgSO_4$, 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

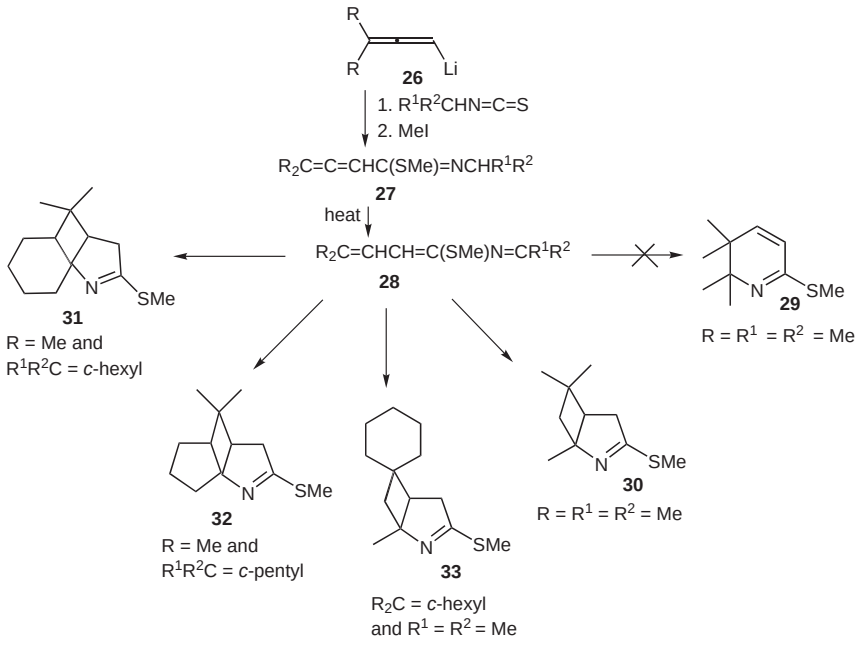
As shown in Scheme 3 the azatriene **12** obtained from the reaction between 3-methyl-1,2-butadienyllithium **10** and methyl or ethyl isothiocyanate gives dihydropyridine **13** upon strong heating. Using 3-methyl-1,2-butadienyllithium and *i*-propyl isothiocyanate ($R^1 = R^2 = Me$) the azatriene **28** ($R = R^1 = R^2 = Me$) 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 cyclobutanopyrroline **30** as the only product in excellent overall yield.[18,26] The analogs **31**, **32**, and **33** are obtained with good overall yields from syntheses with geminally disubstituted allenyllithiums and isopropyl or cycloalkyl isothiocyanates.[14,27] 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(1*H*) 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 $Me_2C=CHCH=C(SMe)N=C(CH_2)_5$ affording $H_2C=C(Me)CH=CHC(SMe)=N$-cyclohexyl, electrocyclization of the latter to the 1,2-dihydropyridine and elimination of methane.[27]

1,6,6-Trimethyl-3-methylthio-2-azabicyclo3.2.0]-hept-2-ene (30, Scheme 8)[26]

a. Methyl *N*-Isopropyl-4-methyl-2,3-pentadienimidothioate, $Me_2C=C=CHC(SMe)=NCHMe_2$ (**27**)

3-Methyl-1,2-butadiene (4.9 g, 0.07 mol) was added to a solution of BuLi (0.05 mol) in hexane (32 mL) and THF (70 mL) cooled at –50 °C. The mixture was stirred for 30 min at –10 to –15 °C and then cooled to –95 °C. *i*-PrSCN (5.4 g, 0.05 mol) was added and the temperature was allowed to rise over 20 min to –55 °C. MeI (9.8 g, 0.07 mol) was added and the temperature was allowed to rise to 5 °C. After addition of water (50 mL), extraction with Et_2O, and drying over K_2CO_3, the solvents were removed under



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 = R^1 = R^2 = Me)

Heating of **31** 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-azabicyclo3.2.0]hept-2-ene (**30**)

Azatriene **28** (R = R^1 = R^2 = 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 ^{1}H NMR spectroscopy After disappearance of the CH= signals the product was isolated by vacuum distillation. If compound **28** with R = Me and R^1R^2C = $(CH_2)_5C$ was heated at ca. 280 °C for 10–15 min, appreciable amounts of 1-cyclohexyl-5-methyl-2(1*H*) 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 Me_2C=CHCH=C(SMe)N=C$(CH_2)_5$ affording H_2C=C(Me)CH=CHC(SMe)=N*c*-hex, electrocyclization of the latter to the 1,2-dihydropyridine and elimination of methane.[27]

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.[20] It can be completed by stirring

Table 2 Procedures for the Directed Synthesis of 3-Substituted 2-Aminothiophenes **39** (Scheme 9)[20,]

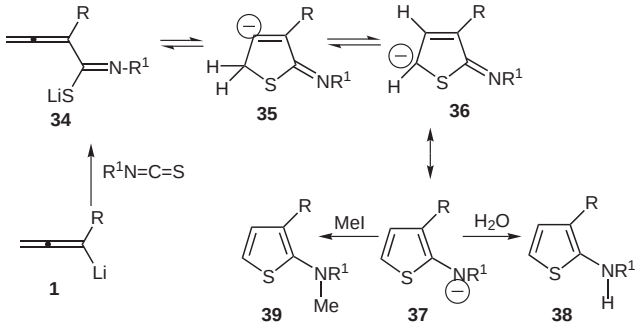
Method[a]	R	R^1	Yield (%)[b]	Method[a]	R	R^1	Yield (%)[b]
A	MeO	Me	32	E	MeO	2-FPh	66
B	MeO	Me	61	E	MeO	2-ClPh	67
E	MeO	Me	75	E	MeO	2-BrPh	69
E	MeS	Me	67	C	MeO	3-ClPh	70
C	MeO	Et	70	E	MeO	3-ClPh	79
A	MeO	Ph	70	E	MeO	4-FPh	76
A	MeO	3-MePh	41	E	MeO	4-ClPh	63
A	MeO	4-MePh	46	A	MeO	3,4-Cl_2Ph	76
A	MeO	2,6-Me_2Ph	73[c]	C	Me	Me	61
A	MeO	3-F_3CPh	71	D	Me	Me	42
E	MeO	4-F_3CPh	68	D	Et	Me	60
E	MeO	4-Me_2NPh	31				

[a] 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 powdered *t*-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 *t*-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 *t*-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 Me_2SO_4 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 *t*-BuOH (1 equiv) in THF and *t*-BuOK (1 equiv) in DMSO (30 mL). After 30 min at 25 °C excess MeI was added at 0 °C, followed by heating.

[b] Not optimized.

[c] *N*-(2,6-Dimethylphenyl)-*N*-[3-methoxy-5-methyl-2(5*H*)-thiophenyliden]amine was obtained instead of the expected *N*-(2,6-dimethylphenyl)-3-methoxy-*N*-methyl-2-thiophenamine.

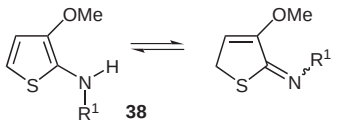
the reaction mixture for a limited period at temperatures above 0 °C. Subsequent addition of water or methyl iodide affords the aminothiophenes **38** or **39**, respectively.[20,28,29] Yields are high in the cases of R^1 = Ph, 3,4-$Cl_2C_6H_4$ and 3-$F_3CC_6H_4$ and moderate if R^1 = 3-MeC_6H_4 and 4-MeC_6H_4 (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**.



R = OMe; R^1 = Alkyl, Ph, 2-, 3-, 4-subst.-Ph
R = Alkyl;R^1 = alkyl
R = SMe; R^1 = Me, Ph

Scheme 9

N-Methyl- or *N*-phenylaminothiophenes **38** show amimo-imino tautomerism, the first examples of this kind of isomerism (Scheme 10). The ratio of the tautomers depends upon the solvent. In CCl_4–$CDCl_3$ (1:1) and in neat $CDCl_3$ the very oxygen-sensitive imino form of **38** (R^1 = Me) predominates (ratio imino/amino approximately 7:15, respectively. In the case of **38** (R^1 = Ph), the ratio of amino/imino is 10:7 in neat $CDCl_3$. Replacement of these solvents by acetone-d_6 causes a strong shift toward the amino tautomer (amino/imino 33:1). Compounds **42** having a methylthio group in the 3-position exist only in the amino form.[29,30]



R^1 = Me or Aryl

Scheme 10

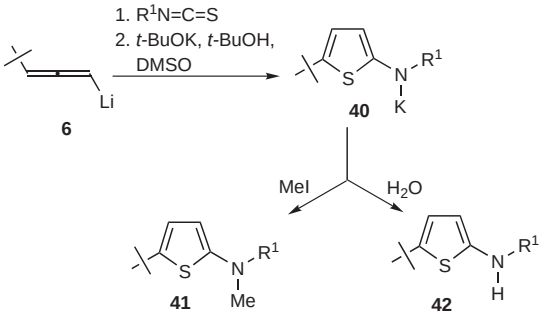
3-Methoxy-*N*-methyl-*N*-phenyl-2-thiophenamine (39, Method A, Scheme 9)[20]

A solution of lithiomethoxyallene (0.06 mol) in hexane (37 mL) and THF (40 mL) was prepared by adding methoxyallene (0.07 mol) at –80 °C to a solution of BuLi (0.06 mol) and subsequently allowing the temperature to rise to –50 °C. The resulting solution was cooled again to ca. –100 °C, after which a mixture of PhNCS (6.8 g, 0.05 mol) and THF (20 mL) was added over a few seconds without external cooling. The red or purple solution of **34** was heated for 30 min at 40 °C, then MeI (11.4 g, 0.08 mol) was added at 0 °C, followed by heating at 40 °C over 15 min. Water (50 mL) was added followed by extraction with Et_2O. The organic solution was concentrated under reduced pressure after drying. Distillation through a short column gave thiophene **39** (bp ca. 120 °C/0.5 Torr, n_D^{20} 1.6135) in 70% yield.

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

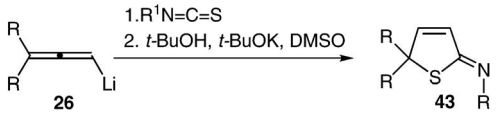
The reaction mixture obtained by the addition of phenyl isothiocyanate to lithiomethoxyallene (cf. preceding procedure) was allowed to reach 0 °C, then water (100 mL) was added followed by stirring for 15 min at r.t. The aminothiophene was isolated as described in the preceding procedure (bp ca. 140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

In analogy with the reactions in Scheme 9 the aminothiophenes **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]



R^1 = alkyl or aryl

Scheme 11



R = alkyl or R_2C = $(CH_2)_5C$; R^1 = alkyl or aryl

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 functionalizations may be attained by replacing lithium by other metals, such as zinc, titanium, and aluminium.[33–36] Remarkably, reactions of lithiated allenes with isothiocyanates in most cases afford allenic thioimidates with very high selectivities, making these metal-metal exchanges,

for which stochiometric amounts of halides or other derivatives of these metals are required, unnecessary. The ready access to these allenic thioimidates allows a convenient approach to the heterocyclic systems mentioned in the preceding sections. The 2,3-dihydropyridines are scarcely studied.[37–41] Some of the dihydropyridines 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 methoxyallene or other allenic ethers $H_2C=C=CHOR$ afford heterocyclic compounds containing the OR substituent. The OCH(Me)OEt substituent, which is introduced when using the readily available[1] $H_2C=C=CHOCH(Me)OEt$, 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 access to 2,3-dienamides,[42,43] their cyclization products, the 2-(5*H*)-furanylidenamines,[43] and 2-*O*-silylated quinolines.[44] These and the above-mentioned research are in progress.[45]

Several acetylenic compounds from which allenic carbanions can be generated have been incorporated in the reactions with isothiocyanates, leading to new families of functionalized pyrroles, dihydropyridines, quinolines, thietanes, cyclobutenes, etc.[20,46]

References

(1) Brandsma, L. *Synthesis of Acetylenes Allenes and Cumulenes Methods and Techniques*; Elsevier: Amsterdam, **2004**, cf. preceding edition Elsevier: Amsterdam **1981**.
(2) Brandsma, L.; Zwikker, J. W. *Science of Synthesis*, Vol. 8; Thieme: Stuttgart, planned to appear in **2004**.
(3) Epsztein, R. In *Comprehensive Carbanion Chemistry*. *Part B. Selectivity in Carbon-Carbon Bond Forming Reactions*; Buncel, E.; Durst, T., Eds.; Elsevier: Amsterdam, **1984**, 107.
(4) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 916.
(5) Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 609.
(6) Zimmer, R. *Synthesis* **1993**, 165.
(7) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; Wiley: New York, **1984**.
(8) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067.
(9) Fall, Y.; Gomez, G.; Fernandez, C. *Tetrahedron Lett.* **1999**, *40*, 8307.
(10) Breuil-Desvergnes, V.; Compain, P.; Vatele, J.-M.; Goré, J. *Tetrahedron Lett.* **1999**, *40*, 8789.
(11) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12.
(12) Breuil-Desvergnes, V.; Goré, J. *Tetrahedron* **2001**, *57*, 1939, 1951.
(13) de Jong, R. L. P.; Verkruijsse, H. D.; Brandsma, L. In *Perspectives in the Organic Chemistry of Sulfur*; Zwanenburg, B.; Klunder, A. J. H., Eds.; Elsevier: Amsterdam, **1987**, 105.
(14) Unpublished results from the author's laboratory.
(15) (a) Nedolya, N. A.; Brandsma, L.; Trofimov, B. A. *Zh. Obshch. Khim.* **1996**, *66*, 2042. (b) Nedolya, N. A.; Brandsma, L.; Trofimov, B. A. *Khim. Geterotsikl. Soedin.* **1996**, 917. (c) Nedolya, N. A.; Brandsma, L.; Trofimov, B. A. *Russ. Chem. Bull.* **1996**, *45*, 2670. (d) Nedolya, N. A.; Brandsma, L.; Trofimov, B. A. *Dokl. Akad. Nauk.* **1996**, *350*, 68. (e) Nedolya, N. A.; Brandsma, L.; Zinov'eva, V. P.; Trofimov, B. A. *Russ. J. Org. Chem.* **1997**, *33*, 80. (f) Nedolya, N. A.; Brandsma, L.; Trofimov, B. A. *Russ. J. Org. Chem.* **1998**, *34*, 1494.
(16) (a) Nedolya, N. A.; Brandsma, L.; Schlyakhtina, N. I.; Fedorov, S. V.; Klyba, L. V. *Zh. Org. Khim.* **2002**, *38*, 957. (b) Nedolya, N. A.; Schlyakhtina, N. I.; Klyba, L. V.; Ushakov, I. A.; Fedorov, S. V.; Brandsma, L. *Tetrahedron Lett.* **2002**, *43*, 9679. (c) Nedolya, N. A.; Brandsma, L.; Schlyakhtina, N. I.; Fedorov, S. V. *Khim. Geterotsikl. Soedin.* **2002**, 707.
(17) Nedolya, N. A.; Brandsma, L.; de Lang, R.-J.; Trofimov, B. A. *Russ. J. Org. Chem.* **1997**, *33*, 580.
(18) Brandsma, L.; Nedolya, N. A.; Verkruijsse, H. D.; Owen, N. L.; Du, Li.; Trofimov, B. A. *Tetrahedron Lett.* **1997**, *38*, 6905.
(19) Nedolya, N. A.; Brandsma, L.; Verkruijsse, H. D.; Tarasova, O. A.; Trofimov, B. A. *Tetrahedron Lett.* **1998**, *39*, 2409.
(20) Nedolya, N. A. *Dissertation*; Utrecht University: The Netherlands, **1999**.
(21) Brandsma, L.; Nedolya, N. A.; Trofimov, B. A. *Russ. Chem. Bull.* **2000**, *49*, 1634.
(22) McNab, H.; Monahan, L. C. *The Synthesis Reactivity and Physical Properties of Substituted Pyrroles*, *In the Series The Chemistry of Heterocyclic Compounds*, Part 2; Taylor, E. C., Ed.; John Wiley & Sons: New York, **1992**, 525.
(23) (a) Darnault, G.; Saquet, M.; Thuiller, A. *Chem. Ind. (London)* **1983**, 391. (b) Ried, W.; Weidemann, P. *Chem. Ber.* **1971**, *104*, 3329. (c) Reischl, W.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6115.
(24) (a) Brandsma, L.; Nedolya, N. A.; de Lang, R.-J.; Trofimov, B. A. *Russ. Chem. Bull.* **1996**, *45*, 2873. (b) Brandsma, L.; Nedolya, N. A.; de Lang, R.-J.; Trofimov, B. A. *Chem. Heterocycl. Compd. (N.Y., NY, U. S.)* **1997**, *33*, 491. (c) Nedolya, N. A.; Brandsma, L.; de Lang, R.-J.; Trofimov, B. A. *Russ. J. Org. Chem.* **1997**, *33*, 1361.
(25) Nedolya, N. A.; Brandsma, L.; Tarasova, O. A.; Klyba, L. V.; Sinegovskaya, L. M.; Trofimov, B. A. *Russ. J. Org. Chem.* **1999**, *35*, 928.
(26) (a) Brandsma, L.; Nedolya, N. A.; van der Kerk, A. C. H. T. M.; Heerma, W.; Lutz, E. T. H. G.; de Lang, R.-J.; Afonin, A. V.; Trofimov, B. A. *Russ. Chem. Bull.* **1997**, *46*, 832. (b) Nedolya, N. A.; Brandsma, L.; van der Kerk, A. C. H. T. M.; Heerma, W.; Lutz, E. T. H. G.; Afonin, A. V.; de Lang, R.-J.; Trofimov, B. A. *Russ. J. Org. Chem.* **1997**, *33*, 1359. (c) Brandsma, L.; Nedolya, N. A.; Heerma, W.; van der Kerk, A. C. H. T. M.; Lutz, E. T. H. G.; de Lang, R.-J.; Afonin, A. V.; Trofimov, B. A. *Chem. Heterocycl. Compd. (N.Y., NY, U.S.)* **1997**, *33*, 493.
(27) Nedolya, N. A.; Brandsma, L.; Trofimov, B. A. *Khim. Geterotsikl. Soedin.* **2002**, 1396.
(28) Brandsma, L.; Nedolya, N. A.; Tarasova, O. A.; Klyba, L. V.; Sinegovskaya, L. M.; Trofimov, B. A. *Dokl. Akad. Nauk.* **1997**, *357*, 350.
(29) Brandsma, L.; Tarasova, O. A.; Vvedensky, V. Yu.; de Jong, R. L. P.; Verkruijsse, H. D.; Klyba, L. V.; Nedolya, N. A.; Trofimov, B. A. *Russ. J. Org. Chem.* **1999**, *35*, 1228.
(30) Brandsma, L.; Vvedensky, V. Yu.; Nedolya, N. A.; Tarasova, O. A.; Trofimov, B. A. *Tetrahedron Lett.* **1998**, *39*, 2433.

(31) Tarasova, O. A.; Klyba, L. V.; Vvedensky, V. Yu.; Nedolya, N. A.; Trofimov, B. A.; Brandsma, L.; Verkruijsse, H. D. *Eur. J. Org. Chem.* **1998**, 253.
(32) Nedolya, N. A.; Brandsma, L.; Schlyakhtina, N. I.; Lazarev, I. M.; Albanov, A. I.; Zinchenko, S. V.; Klyba, L. V. *Arkivoc* **2001**, *2 [Part 3 (IX)]*, 12.
(33) Mercier, F.; Epsztein, R.; Holand, S. *Bull. Soc. Chim. Fr.* **1972**, 690.
(34) Mercier, F.; Epsztein, R. *J. Organometal. Chem.* **1976**, *108*, 165.
(35) Pearson, N. R.; Hahn, G.; Zweifel, G. *J. Org. Chem.* **1982**, *47*, 3364.
(36) Hoppe, D.; Gonschorrek, C. *Tetrahedron Lett.* **1987**, *28*, 785.
(37) Lasne, M.-C.; Ripoll, J.-L.; Guillemin, J.-C.; Denis, J.-M. *Tetrahedron Lett.* **1984**, *25*, 3847.
(38) Meyers, A. I.; Betrus, B. J.; Ralhan, N. K.; Rao, K. B. *J. Heterocycl. Chem.* **1964**, *1*, 13.
(39) Meyers, A. I.; Schneller, J.; Ralhan, N. K. *J. Org. Chem.* **1963**, *28*, 2944.
(40) Fuks, R.; Merenyi, R.; Viehe, H. G. *Bull. Soc. Chim. Belg.* **1976**, *83*, 147.
(41) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141.
(42) Nedolya, N. A.; Brandsma, L.; Trofimov, B. A. *Russ. J. Org. Chem.* **1997**, *33*, 557.
(43) (a) Nedolya, N. A.; Brandsma, L.; Schlyakhtina, N. I.; Albanov, A. I. *Chem. Heterocycl. Compd.* **2001**, *37*, 1173. (b) Nedolya, N. A.; Schlyakhtina, N. I.; Zinov'eva, V. P.; Albanov, A. I.; Brandsma, L. *Tetrahedron Lett.* **2002**, *43*, 1569.
(44) Nedolya, N. A.; Brandsma, L.; Trofimov, B. A. *Mendeleev Commun.* **1997**, 92.
(45) Nedolya, N. A.; Brandsma, L. *Zh. Org. Khim.* **2003**, *39*, 645.
(46) (a) Brandsma, L.; Nedolya, N. A.; Trofimov, B. A. *Eur. J. Org. Chem.* **1999**, 2663. (b) Brandsma, L.; Nedolya, N. A.; Verkruijsse, H. D.; Trofimov, B. A. *Chem. Heterocycl. Compd. (N.Y., NY, U.S.)* **2000**, *36*, 876. (c) Nedolya, N. A.; Brandsma, L.; Tolmachev, S. V.; Albanov, A. I. *Khim. Geterotsikl. Soedin.* **2001**, 394. (d) Nedolya, N. A.; Brandsma, L.; Schlyakhtina, N. I.; Tolmachev, S. V. *Chem. Heterocycl. Compd.* **2001**, *37*, 366. (e) Brandsma, L.; Spek, A. L.; Trofimov, B. A.; Tarasova, O. A.; Nedolya, N. A.; Afonin, A. V.; Zinchenko, S. V. *Tetrahedron Lett.* **2001**, *42*, 4687. (f) Brandsma, L.; Nedolya, N. A.; Tolmachev, S. V. *Chem. Heterocycl. Compd.* **2002**, *38*, 54. (g) Nedolya, N. A.; Brandsma, L.; Tolmachev, S. V. *Khim. Geterotsikl. Soedin.* **2002**, 843. (h) Nedolya, N. A.; Brandsma, L.; Tolmachev, S. V. *Zh. Org. Khim.* **2002**, *38*, 948. (i) Nedolya, N. A.; Brandsma, L.; Schlyakhtina, N. I. *Zh. Org. Khim.* **2002**, *38*, 1113. (j) Tarasova, O. A.; Brandsma, L.; Nedolya, N. A.; Afonin, A. V.; Ushakov, I. A.; Klyba, L. V. *Zh. Org. Khim.* **2003**, *39*, 1521. (k) Tarasova, O. A.; Brandsma, L.; Nedolya, N. A.; Ushakov, I. A.; Dmitrieva, G. V.; Koroteeva, T. V. *Zh. Org. Khim.* **2004**, *40*, 140.