Unsaturated Carbanions, Heterocumulenes and Thiocarbonyl Compounds – New Routes to Heterocycles

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The combination of metallated unsaturated compounds and heterocumulenes or thiocarbonyl compounds offers several possibilities for further reactions, especially those producing heterocyclic systems. This review covers research in this field carried out in the author's group at Utrecht University over the past two decades. The starting compounds involved in these investigations are mainly olefinic, acetylenic and allenic derivatives, isothiocyanates, carbon disulfide and some non-enethiolisable thiocarbonyl compounds.

Introduction and General Principles

For the regioselective deprotonation of unsaturated compounds — the first step in the syntheses reviewed — a variety of strongly basic reagents and solvents are available. The great majority of these unsaturated systems can be converted into the desired anionic intermediates by a suitable combination of base and solvent. The so-called superbases[1] — mixtures of equimolar amounts of *n*BuLi and heavier alkali metal *tert*-alkoxides — have found useful applications in the removal of protons of low kinetic acidity. The various methods for deprotonation are amply illustrated by experimental procedures on a preparative scale available in various laboratory manuals.[2]

Anionic species formed by the removal of allylic, propargylic or allenic protons can react in two mesomeric "forms" with electrophiles, giving rise to a mixture of compounds derived from both forms. The ratio of the derivatives is, in general, not easily predictable or explainable. It depends on the nature of the electrophile, the counter-ion (Li, Na, K, MgHal etc.) and the polarity of the solvent, while steric and electronic effects of substituents close to the anionic site may also have a strong influence.[3] However, synthetically useful selectivities have been found in many reactions involving heterocumulenes and thiocarbonyl compounds. The second step in most of the syntheses described in this review is the attack of the anionic intermediate on the *central* atom of the substrate (carbophilic attack in the case of compounds containing a C=S group). Undesired reactions such as transmetallation can be suppressed or avoided by replacing the counter-ion in the metallated unsaturated compound by another metal. This intermediary adduct may then be allowed to react in various different ways:

aqueous hydrolysis, usually affording a carbodithioate, an *N*-monosubstituted carboxamide, -thioamide or -sulfinamide in the case of heterocumulenes;

treatment with an alkyl halide, resulting in the formation of an alkyl carbodithioate, an *N*,*N*-disubstituted carboxamide (*N*-alkylation was found in the few cases investigated by us), a thioimidate (*S*-alkylation) or an *N*,*N*-disubstituted sulfinamide (*N*-alkylation);

other operations that produce heterocyclic products.

I. Reactions between Heterocumulenes and sp-Metallated Acetylenic or sp^2- or sp^3-Metallated Olefinic Derivatives

Analogous with the known reaction between heterocumulenes and alkyl-, aryl- or hetaryllithium or Grignard compounds,[4] a number of metallated 1-alkynes and olefinic compounds have been treated with isothiocyanates, isocyanates, sulfinylamines or carbon disulfide, with sub-

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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Table 1. Reaction of metallated acetylenes and olefins with heterocumulenes[a]

RLi or RK	Heterocumulene, operations	Temp.[b] (°C)	Product[c]	Ref.
MeC≡CLi	PhN=C=O, H_2O + H^+	−40 → 10	RC(=O)NHPh	[2c]
	PhN=C=O, Me_2SO_4 + DMSO	−40 → 10	RC(=O)NMePh	[5]
*t*BuC≡CLi	MeN=C=S, H_2O + H^+	−10 → 10	RC(=S)NHMe	[2c]
MeC≡CLi	PhN=C=S, MeI	20 → 40	RC(SMe)=NPh[d]	[5]
*t*BuC≡CLi	PhN=S=O, H_2O + H^+	−10 → 0	RS(=O)NHPh	[2c]
H_2C=C(K)OEt[e]	MeN=C=S, MeI	−90 → −50	RC(SMe)=NMe	[6]
	MeN=C=S, H_2O + H^+	−90 → −50	RC(=S)NHMe	[5]
H_2C=C(K)SEt[e]	$MgBr_2$·Et_2O, allylN=C=S, MeI	0 → 20	RC(SMe)=N-allyl	[5]
	MeN=C=S, MeI	−90 → −50	RC(SMe)=NMe	[6]
	LiBr, nPrN=C=O, H_2O + H^+	−90 → −50	RC(=O)NH-*n*Pr	[5]
	LiBr, nPrN=C=O, MeI + DMSO	−90 → −50	RC(=O)NMe-*n*Pr	[5]
H_2C=CHCH_2K[e]	LiBr, MeN=C=S, H_2O + H^+	−90 → −60	RC(=S)NHMe	[5]
	LiBr, CS_2, MeI	−110 → −20	H_2C=CHCH=C$(SMe)_2$	[7]
	LiBr, PhN=S=O, H_2O + H^+	−110 → −10	RS(=O)NHPh	[5]

[a] Solvent: THF/hexane, ≈1:1. − [b] Temp. of addn. reaction. − [c] Isolated yields good to excellent. − [d] With catal. amounts of CuBr the addition proceeds at lower temperature and yields are ≈15% higher. − [e] Prepared from RH and a 1: 1 molar mixture of *n*BuLi and *t*BuOK, see ref. 2b.

sequent hydrolysis or alkylation. Table 1 gives some representative examples.

The products obtained by hydrolysis of the adducts formed by the reactions of isocyanates, isothiocyanates and sulfinylamines are *N*-monosubstituted carboxamides, the analogous thiocarboxamides and sulfinamides, respectively. The adducts arising from reactions with isocyanates undergo exclusive *N*-alkylation with alkyl halides, even under strongly polar conditions (DMSO as co-solvent and *t*BuOK as additive). In the case of isothiocyanates, *syn*- and *anti*-thioimidates are formed by alkylation at sulfur.

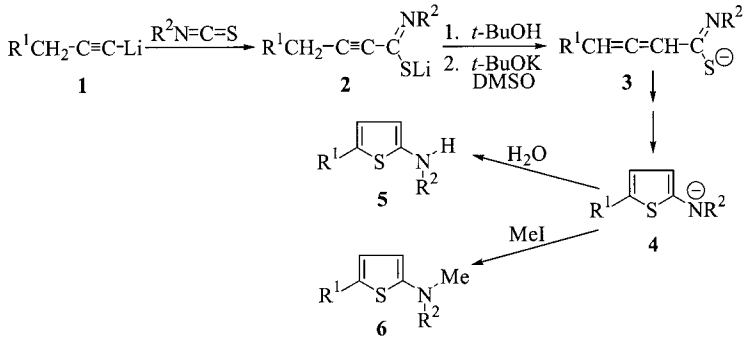
The initially formed adducts, such as H_2C=CHCH_2C-(=S)SLi, from the reactions between allylic anions and carbon disulfide are immediately converted under the strongly basic conditions into geminal dithiolates, H_2C=CHCH=C$(SLi)_2$, which yield ketene *S,S*-acetals upon alkylation.[7]

II. Syntheses Involving Alkynyllithiums and Isothiocyanates

The addition of terminally lithiated acetylenes **1** to isothiocyanates is the first step in a novel one-pot synthesis[8] of the 5-substituted 2-aminothiophenes **5** and **6** (Scheme 1).

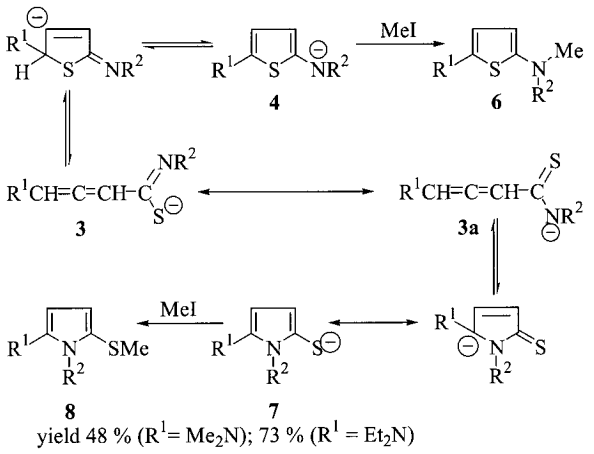
A solution of adduct **2** was treated with a solution of *t*BuOK in DMSO; under these conditions the allenic isomer **3** is assumed to be formed. This was then able to undergo ring-closure with the ultimate formation of amide **4**, hydrolysis and methylation of which afforded the aminothiophenes **5** and **6** in fair to good yields.

In reactions with some metallated propargylic amines, the pyrrole derivatives **8** were isolated in fair to good yields when the temperature was increased to over 40 ° C prior to methylation.[9] This surprising result may be explained by



Scheme 1. 5-Substituted 2-aminothiophenes from acetylenes and isothiocyanates

assuming an equilibrium between the anions **4** and **7**, which may result from two ring-closure modes in the resonance hybrid **3** ⇄ **3a**. (Scheme 2). Alternatively, a Dimroth rearrangement of **4** to **7** would also explain the formation of **8.**



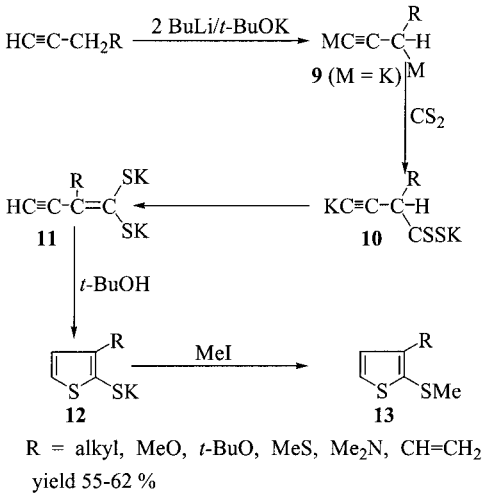
Scheme 2. 2,5-Disubstituted pyrroles or 2,5-bis(dialkylamino)thiophenes from propargylic amines and isothiocyanates

III. Treatment of 1,3-Dimetallated Acetylenes with Heterocumulenes and Non-Enethiolisable Dithioesters

It has been reported[10,11] that a number of electrophiles react selectively with the most strongly basic centre in 1,3-dimetallated acetylenes. This regioselectivity is also evident in reactions with carbon disulfide, isothiocyanates and a number of non-enethiolisable thiocarbonyl compounds and has been applied in various syntheses of 2,3-disubstituted thiophenes and some other cyclic systems. In many of these syntheses the acetylenic starting compound is metallated with the superbase reagent BuLi-*t*BuOK, either because dimetallation with BuLi alone proceeds too slowly, or in order to ensure a higher reactivity of the dimetallated acetylene.

III-1. Reactions with Carbon Disulfide

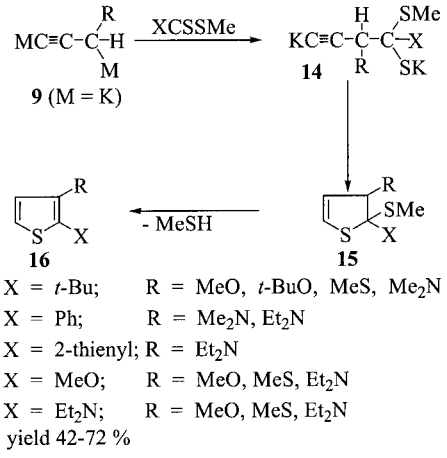
Reactions between 1,3-dipotassium acetylenes and carbon disulfide were carried out by addition of carbon disulfide in one portion to a slight excess of a solution or suspension of the dimetallated acetylene **9** (M = K) at temperatures below −70 °C. If methyl iodide was added shortly after the very fast reaction, the ketene *S,S*-acetals $HC{\equiv}CC(R){=}C(SMe)_2$ could be isolated in good yields, which may be indicative of the presence of the geminal dithiolates **11**, formed from the initial carbodithioates **10**, as intermediates (Scheme 3). Cyclisation of the dithiolate was achieved by the addition of *tert*-butyl alcohol, which serves as a provider of the necessary proton. The resulting thiophenethiolate **12** was methylated to produce the 3-substituted 2-methylmercaptothiophenes **13** in 50−60% yields.[12,17]



Scheme 3. 3-Substituted 2-methylthiothiophenes from dipotassium acetylenes and carbon disulfide

III-2. Reactions with Non-Enethiolisable Thiocarbonyl Compounds

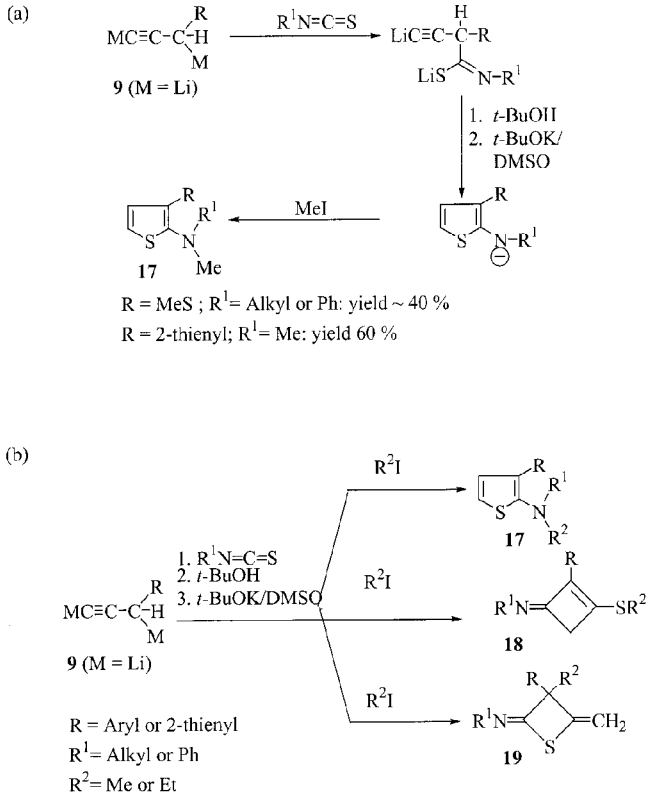
A number of 2,3-disubstituted thiophenes **16** have been obtained in fair to good yields from reactions between dipotassium acetylenes **9** (M = K) and non-enethiolisable thiocarbonyl compounds[13] (Scheme 4). The formation of the thiophenes is envisaged as a carbophilic attack of the most strongly basic propargylic centre at the C=S group, followed by the sequential ring-closure of adduct **14** and the elimination of thiolate from **15**. From reactions involving dimetallated acetylenic *hydrocarbons* (R = alkyl), tarry products were mainly obtained, while in reactions between dipotassium acetylenes and 2-thienyl-$CSSCH_3$ the main reaction was transmetallation at the 5-position of the thiophene ring. This reaction could be suppressed effectively by the initial replacement of K by Li, by addition of LiBr. Several of these 2,3-disubstituted thiophenes are inaccessible or not easily accessible otherwise.



Scheme 4. 2,3-Disubstituted thiophenes from dipotassium acetylenes and non-enethiolisable dithioesters

III-3. Reactions with Isothiocyanates

The treatment of dimetallated acetylenes with isothiocyanates was investigated only preliminarily.[14] Following the usual procedure for the synthesis of heterocyclic systems, various dilithiated acetylenes **9** (M = Li) were treated at low temperatures with a number of isothiocyanates, after which *tert*-butyl alcohol and a solution of *t*BuOK in DMSO were added successively, followed by final treatment with alkyl iodide. The expected 2-*N,N*-disubstituted thiophenes **17** (Scheme 5a) were indeed obtained from a number of these reactions, but in other cases appreciable amounts of the cyclobutene **18** and/or the thietane derivatives **19** were isolated, while some combinations of acetylenes and isothiocyanates afforded only one of the three cyclic products (Scheme 5b): the dilithiation of 2-methyl-5-propargylthiophene **9** (R = 2-methylthienyl) and treatment with MeN=C=S, *t*BuN=C=S or PhN=C=S, followed by MeI, gave rise to **17**, **18** or **19**, respectively, in good yields. The mechanism for the formation of **18** and **19** has not yet been investigated and our proposal is based largely on speculation.[14]



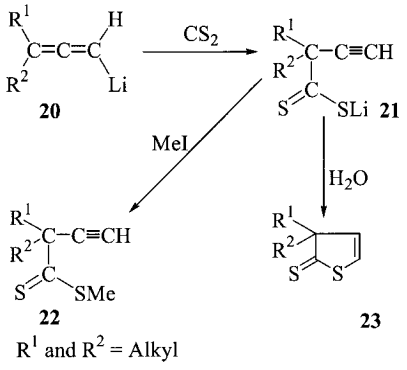
Scheme 5a + b. Derivatives of thiophene, thietane or cyclobutene from dilithiated acetylenes and isothiocyanates

IV. Reactions of Acetylenic-Allenic Carbanions with Carbon Disulfide and Non-Enethiolisable Dithioesters

This section deals with syntheses of a variety of heterosubstituted thiophene derivatives. In all syntheses the initial step is a highly regioselective reaction between the heterocumulene or thiocarbonyl compound and the carbanionic intermediate generated from an acetylenic or allenic derivative, reacting either only in the acetylenic or only in the allenic form. A comparison of the initial reactions between one particular species and different substrates reveals striking differences in regiochemistry. For example, whereas the potassium derivative of $CH_3C{\equiv}CNEt_2$ exclusively gives the allenic adduct with carbon disulfide, in all of its reactions with the dithioesters XC(=S)SMe (X = Ph, 2-thienyl, *t*Bu, RO, RS, R_2N) it reacts in the acetylenic form. The reaction between $Me_2C{=}C{=}CHLi$ and isocyanates or isothiocyanates affords only the expected allenic carboxamides[15] or analogous thioamides,[5] whereas treatment with CS_2 results in the exclusive formation of $Me_2C(CSSLi)C{\equiv}CH$.[16] Some of these reactions have only limited application in the synthesis of heterocycles because of their unsatisfactory selectivity.

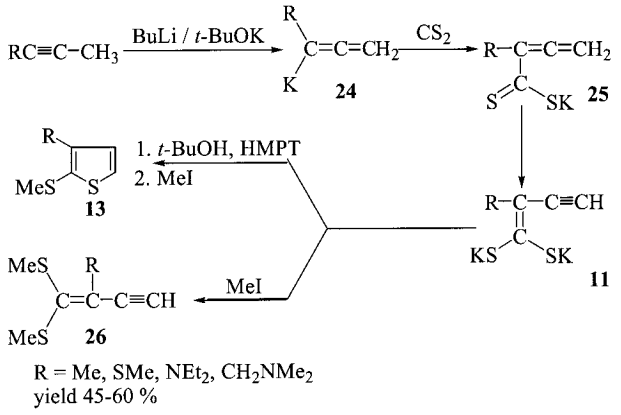
IV-1. Reactions with Carbon Disulfide

A number of terminally lithiated allenes **20** have been reported to react with carbon disulfide to give, after addition of methyl iodide, the acetylenic dithioesters **22** as the only products.[16] The intermediary adducts **21** could be converted into the dithiolactones **23** under suitable conditions (Scheme 6).



Scheme 6. Dithiolactones or acetylenic dithioesters from lithiated allenes and carbon disulfide

Building on this finding, we investigated the reactions between a number of metallated 2-alkynyl or -allenyl compounds **24** and carbon disulfide.[17,18] Addition of CS_2 at very low temperatures to a suspension or solution of a 100% molar excess of the potassium derivative of the acetylenes or allenes, followed by addition of *tert*-butyl alcohol, a small amount of HMPT (DMSO could presumably also be used) and final methylation with methyl iodide, in most cases gave the 2,3-disubstituted thiophenes **13** in fair yields. If methyl iodide was added immediately after the reaction with CS_2, the ketene *S,S*-acetals **26** were isolated in similar yields (Scheme 7).



Scheme 7. 2,3-Disubstituted thiophenes from potassium derivatives of acetylenes and carbon disulfide

Metallated allenic ethers $H_2C{=}C{=}CHOR'$, or their analogous sulfides and amines give 2,3-disubstituted thiophenes. Alkylallenes, such as n-$C_4H_9CH{=}C{=}CH_2$, are metallated terminally, but the metal derivatives react in the acetylenic form, after which further reaction results in the 2,3-disubstituted thiophenes, by a route analogous to that shown in Scheme 7. Presumably because of steric hindrance, the initial reaction of CS_2 with the intermediates tBuC≡CCH_2K and tBuCH=C=CHK proceeds at the terminal carbon atoms, resulting in 2-*tert*-butyl-5-methylmercaptothiophene. The deprotonation of RCH=C=CHSMe and RC≡CCH_2SMe (R = alkyl) gives RCH=C=C(K)SMe and RC≡CCH(K)SMe, respectively. Both species react in the allenic form to afford two isomeric 2,3,5-trisubstituted thiophenes.[5] By starting with 2,4-diynes $CH_3C{\equiv}C{-}C{\equiv}C{-}R$ it was possible to synthesise a number of otherwise not easily accessible 2-substituted thienothiophenes[18] (see ref.[19]).

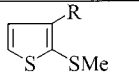
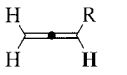
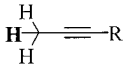
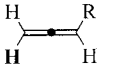
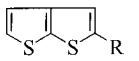
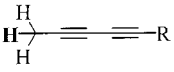
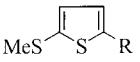
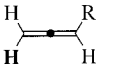
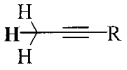
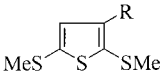
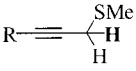
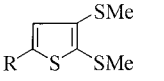
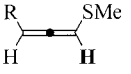
In all cases the yields seem modest, but it should be noted that about 50 mol % of the metallated acetylene or allene is consumed by the very fast subsequent deprotonation of the initial carbodithioate, giving rise to the geminal dithiolate. These results are summarised in Table 2.

The reactions gave large amounts of tarry products with most of the *lithiated* compounds. A very unusual result was obtained when carbon disulfide was added at very low temperatures to a 100 mol % excess of a solution of the lithiated 2-alkyne **27**, with the usual sequence of operations subsequently being carried out.[20] The formation of the ketene *S,S*-acetal **30** can be explained by assuming an attack of the lithiated alkyne at the central carbon atom of the allenic system in the initial adduct **28**, with formation of geminal dithiolate **29** (Scheme 8).

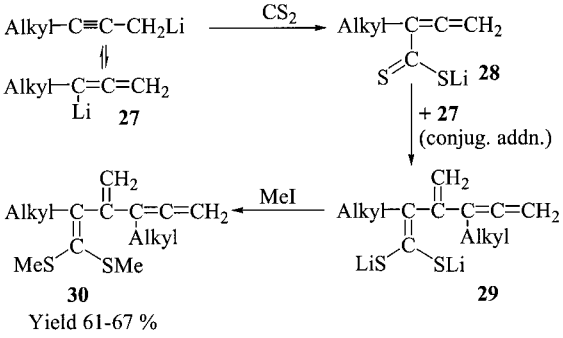
IV-2. Reactions with Non-Enethiolisable Thiocarbonyl Compounds

French investigators have reported the carbophilic reaction of allenylmagnesium bromide $H_2C{=}C{=}CHMgBr$ with thioketones RC(=S)R′ and dithioesters RC(=S)SR′. After treatment with methyl iodide they obtained the acetylenic

Table 2. Thiophenes from potassium derivatives of acetylenes or allenes and carbon disulfide

Thiophene[a]	Starting Compound[b]	R
		O-alkyl, S-alkyl, NMe_2, COOEt
		*prim*-alkyl, NEt_2, Et_2NCH_2, C(Me)=CH_2
		*prim*-alkyl
		*t*-Bu, CH_2NEt_2, Me_2N, Et_2N
		*t*-Bu
		*t*-Bu, Me_3Si
		alkyl
		alkyl

[a] Yields between 40 and 50%; [b] The abstracted proton is indicated in bold.

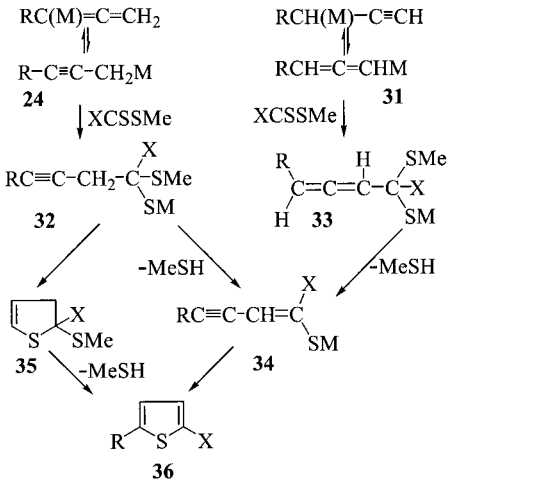


Scheme 8. Treatment of lithiated 2-alkynes with carbon disulfide

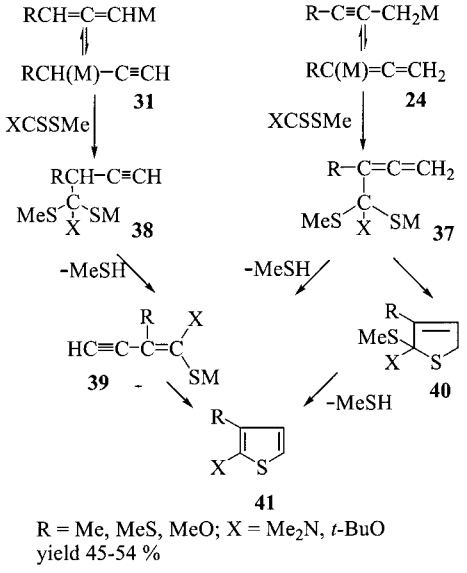
derivatives HC≡CCH_2C(R)(R′)SMe, while aqueous hydrolysis afforded five-membered compounds.[21,22]

We investigated the treatment of the acetylenic-allenic carbanions **24** and **31** with the non-enethiolisable dithioesters XC(=S)SMe (X = *tert*-butyl, phenyl, 2-thienyl or a hetero-substituent). The usual procedure involved addition of the dithioester, at very low temperatures, to a suspension or solution of the metallated acetylene or allene **24** or **31**, followed by the addition of *tert*-butyl alcohol (as a proton donor) and HMPT.[12,23] The initial adducts **32**, **33**, **37** and **38** (Scheme 9 and 10), formation of which could be proved by *S*-methylation at low temperatures, may either undergo

direct cyclisation to the dihydrothiophenes **35** and **40**, or lose methanethiol to give the enynethiolates **34** and **39**. The routes to the thiophene derivatives **36** and **41** are completed by the elimination of methanethiol or by an intramolecular nucleophilic attack of thiolate. The elimination of thiol may proceed under the influence of the lithium *tert*-butoxide (formed during the metallation of the unsaturated starting compound with the *n*BuLi-*t*BuOK couple), although the metallated unsaturated compound may also be responsible in part for this elimination in some cases. The recovery of appreciable amounts of the thiocarbonyl compound, especially R′OC(=S)SMe, in the workup may be indicative of the latter possibility.



Scheme 9. 2,5-Disubstituted thiophenes from metallated acetylenes or allenes and dithioesters



Scheme 10. 2,3-Disubstituted thiophenes from metallated acetylenes or allenes and dithioesters

Our results may be summarised as follows:

• With *t*BuCSSMe (i.e. X = *t*Bu), most of the metallated acetylenes or allenes **24** or **31** reacted regioselectively to afford only the 2,5-disubstituted thiophenes **36** (Scheme 9). Notable exceptions are the reactions of the lithium or potassium derivatives of the allenic ethers **24** (R = OMe) or sulfides **24** (R = SMe), which afford 30:70 mixtures of the 2,3- and 2,5-disubstituted thiophenes **41** and **36**, respectively (Scheme 9 and 10).

• Metallated allenic amines or yneamines **24** (R = Me_2N or Et_2N) reacted exclusively in the acetylenic form to afford the 2,5-disubstituted thiophenes **36** (Scheme 9).

• Most of the reactions with PhCSSMe (X = Ph) and 2-thienylCSSMe (X= 2-thienyl) were not regioselective and gave the 2,3- and 2,5-disubstituted thiophenes in comparable amounts (Scheme 9 and 10). Moreover, in some cases transmetallation at the 5-position of the thiophene ring in the dithioester was the main reaction, giving rise to recovery of most of the dithioester.

• Reactions of metallated acetylenes or allenes with $Me_2NCSSMe$ and $Et_2NCSSMe$ (X = Me_2N or Et_2N) either exclusively gave the 2,3-disubstituted **41** (Scheme 10) or the 2,5-disubstituted thiophenes **36** (Scheme 9).

• Reactions with xanthogenates R′OCSSMe (X = R′O) and trithiocarbonates MeSCSSMe (X = SMe) in many cases gave mixtures of the disubstituted thiophenes **36** and **41**. A remarkable influence of the metal ion on the regiochemistry was observed in the reaction between the metallated propynyl sulfides **24** (R = SMe) and MeSCSSMe (X = MeS). Whereas the potassium derivative of **24** predominantly (>90%) gave the

Table 3. Synthesis of 2,3- or 2,5-disubstituted thiophenes from metallated acetylenes or allenes and dithioesters XCSSMe (see also Scheme 9 and 10)[a]

Metallated compound **24** or **31**	X	2,3-Disubst. (**41**)	2,5-Thioph. (**36**)
MeC≡CCH_2K (**31**)	Me_2N	+	
*n*PrC≡CCH_2K (**31**)	*t*Bu		+
*n*BuCH=C=CHK (**31**)	*t*Bu		+
*t*BuCH=C=CHK (**31**)	*t*Bu		+
$Me_2NC(K)=C=CH_2$ (**24**)	MeS		+
$Et_2NC≡CCH_2K$ (**24**)	*t*BuO	+	
Ph		+	
Et_2N		+	
$Et_2NCH_2C≡CCH_2K$ (**24**)	*t*Bu		+
$Et_2NC≡CC≡CCH_2K$ (**24**)	*t*Bu		+
$MeSC(Li)=C=CH_2$ (**24**)	MeS[b]		+
$MeSC(K)=C=CH_2$ (**24**)	Me_2N	+	
*t*BuO		+	
$MeOC(K)=C=CH_2$ (**24**)	*t*BuO	+	
Me_2N		+	
MeSC≡CC≡CCH_2K (**24**)	*t*Bu	+	

[a] Fair to good yields, based on starting acetylenes or allenes. – [b] In case of the potassium derivative of the allenic sulfide the ratio of 2,3- and 2,5-disubst. thiophene was ≈ 9.

2,3-bis(methylthio)thiophene **41** (R = X = SMe), only the 2,5-isomer **36** (R = X = SMe) was isolated from the reaction with the *lithiated* propynyl sulfide.
Table 3 shows a number of satisfactory results.

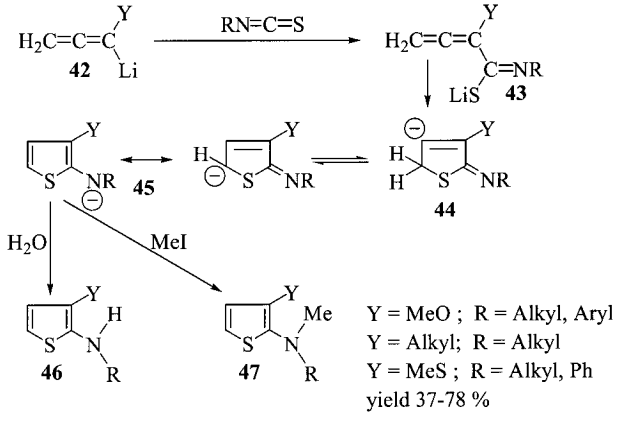
V. Reactions between Acetylene-Allene Carbanions and Isothiocyanates

The first step in the syntheses reviewed in this section is the addition of a mesomeric acetylene-allene carbanion to an isothiocyanate. The adduct can then be allowed/forced to undergo cyclisation, after which further operations provide thiophene or dihydrothiophene derivatives. If a sufficiently reactive alkyl halide is added immediately after the initial addition reaction, a thioimidate is formed by reaction at sulfur. If this intermediate is heated, it may undergo rearrangement/ring-closure reactions, resulting in the formation of 2,3-dihydropyridines, quinolines, cyclobutanopyrrolines or *N*-substituted pyrroles, depending on the structures of the starting compounds.

Most of the addition reactions with isothiocyanates so far investigated by us have been highly regioselective with respect to the reacting centres in the unsaturated anionic species, but extension with other anionic species or isothiocyanates might reveal cases of synthetically unsatisfactory selectivity.

V-1. Syntheses of 2-Aminothiophenes and 2-Imino-2,5-dihydrothiophenes

Regiospecific reactions between 1-lithiated allenic ethers or sulfides and isothiocyanates have provided syntheses of a number of 3-heterosubstituted 2-aminothiophenes (Scheme 11) with fair to good yields.



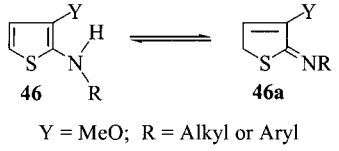
Scheme 11. 3-Substituted 2-aminothiophenes from lithiated acetylenes or allenes and isothiocyanates

The assumed proton-metal (charge) exchange producing the thiophene ring may take place either intramolecularly or by a process of proton donation and abstraction in the presence of *tert*-butyl alcohol and a suitable co-solvent, usually DMSO. Some cyclisations proceeded only if a sufficient amount of *t*BuOK was added. The lithiomethoxyallene **42** (Y = MeO) reacts with various aryl isothiocyanates in the absence of any additive to give the corresponding thiophene derivatives with striking ease. In the cases of certain *meta*-substituted phenyl isothiocyanates, the ring-closure occurred at a significant rate even at temperatures in the region of −50 °C.[24]

The reaction between lithiated 2-alkynes (**42**, Y = alkyl) and *alkyl* isothiocyanates also proceeds with a regioselectivity sufficient to be applicable in the synthesis of 3-alkyl-2-aminothiophenes.[25]

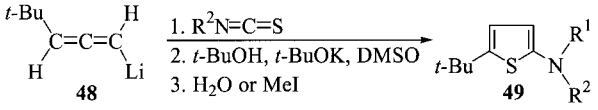
The final steps in the syntheses of **46** and **47** were either simple aqueous workup or *N*-methylation of the intermediate **45**.

N-Monosubstituted thiophenes with methoxy groups at their 3-positions undergo an amino-imino tautomerism[26] (Scheme 12), while the other 3-substituted aminothiophenes exist only as their amino tautomers.



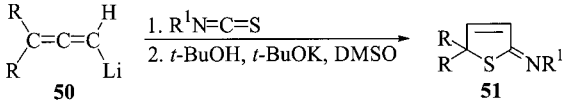
Scheme 12. Imino-amino tautomerism in 3-alkoxy-2-aminothiophenes

A few 2-*N*-mono- and 2-*N,N*-disubstituted thiophenes **49** have been synthesised in fair to good yields starting with *tert*-butylallenyllithium **48** (see Scheme 13),[8] by procedures analogous to those depicted in Scheme 11.



Scheme 13. 5-Substituted 2-aminothiophenes from terminally lithiated allenes and isothiocyanates

Base-catalysed cyclisations of the adducts produced from disubstituted allenyllithiums **50** afforded 2-imino-2,5-dihydrothiophenes **51** in excellent yields[5] (Scheme 14).

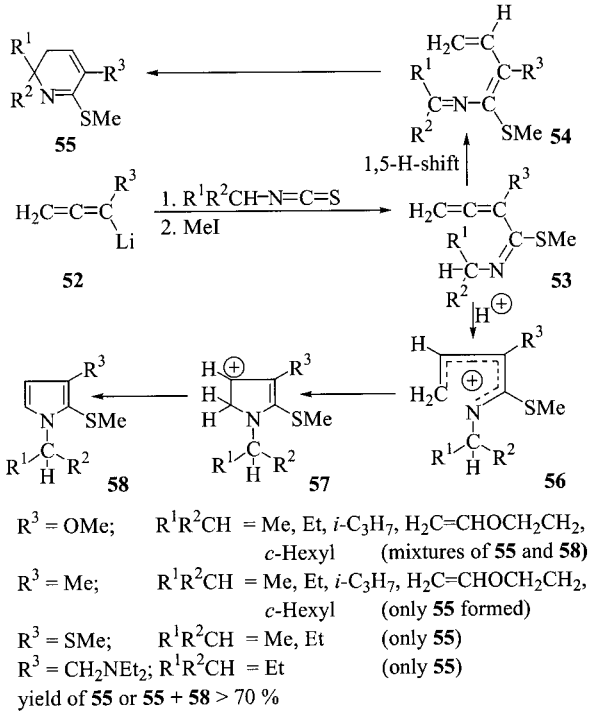


Scheme 14. 2-Imino-2,5-dihydrothiophenes from geminally disubstituted allenes and isothiocyanates

V-2. Formation of 2,3-Dihydropyridines and 1,2,3-Trisubstituted Pyrroles

In Section V-1 (Scheme 11 and 13) it was shown that 3- and 5-substituted 2-aminothiophenes can be synthesised by the treatment of lithiated allenes with isothiocyanates, sub-

sequently forcing the adducts to cyclise by addition of a strongly polar aprotic solvent, in combination in some cases with *t*BuOK and *t*BuOH, and final *N*-alkylation or hydrolysis. In general, this cyclisation does not take place in the absence of these additives, and addition of a reactive alkyl halide results in the *S*-alkylation of the adduct **53** from the lithiated allene **52** and the isothiocyanate. Simple heating of **53** results in most cases in the formation of the 2,3-dihydropyridines **55** (Scheme 15). 2,3-Dihydropyridines are a little known class of compounds.[27−30] Sequential addition of the metallated allene or acetylene to an alkyl isothiocyanate, *S*-alkylation and heating gives access to a variety of 2,3-dihydropyridines, all with *S*-alkyl groups at their 6-positions.[32] The formation of **55** may be explained by assuming a 1,5-sigmatropic H-shift and subsequent electrocyclisation of the fully conjugated azatriene **54**. This could not be detected in the reaction with methyl isothiocyanate (R^1 = R^2 = H), but with other isothiocyanates (one or both of the groups R^1 and R^2 = alkyl), heating of **53** to ≈50 °C resulted in its partial or complete conversion into **54**. Upon heating more strongly, the dihydropyridine **55** was formed.



Scheme 15. 2,3-Dihydropyridines and trisubstituted pyrroles from acetylenes or allenes and isothiocyanates

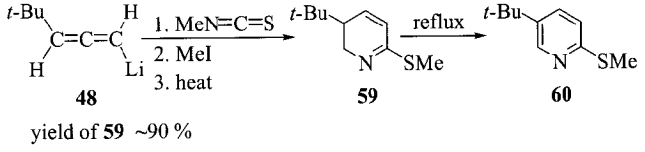
The products obtained from *1-lithiated methoxyallene* **52** (R^3 = OMe; Scheme 15), alkyl isothiocyanates and methyl iodide were found to be *syn-anti* mixtures of the thioimidates **53**. The most simply substituted representative (R^1 = R^2 = H) underwent an exothermic rearrangement upon heating at slightly elevated temperatures, to afford a 75:25 mixture of the pyrrole **58** and the dihydropyridine **55**. Addition of the thioimidate to paraffin oil at ≈150 °C changed the ratio in favour of the 2,3-dihydropyridine (≈40:60).[5]

The ratio of **55** to **58** depended heavily upon the isothiocyanate.[5,24] The dihydropyridine **55** was the predominant (>75%) product arising from reactions involving ethyl, isopropyl, cyclopentyl and cyclohexyl isothiocyanate, while equal amounts of the dihydropyridine and the pyrrole derivative **58** were obtained from the reaction with H_2C=$CHOCH_2CH_2N$=C=S.[32] The mechanism by which the pyrroles **58** are formed is not clear. One possible route involves the addition of a proton to the allenic system, subsequent electrocyclisation of the azacarbenium ion **56** and stabilisation by loss of a proton. Attempts to favour the formation of pyrroles by use of various protic acids did not give clear results.[5]

The 2,3-dihydropyridines **55** and pyrroles **58** could be easily and quantitatively separated by treatment of the mixtures with cold dilute hydrochloric acid.

When other lithiated acetylenic or allenic compounds **52** (R^3 = Me, SMe, CH_2NEt_2) were used as starting materials, a number of 2,3-dihydropyridines were obtained in good yields (Scheme 15). Derivatives of pyrrole were not formed.[32]

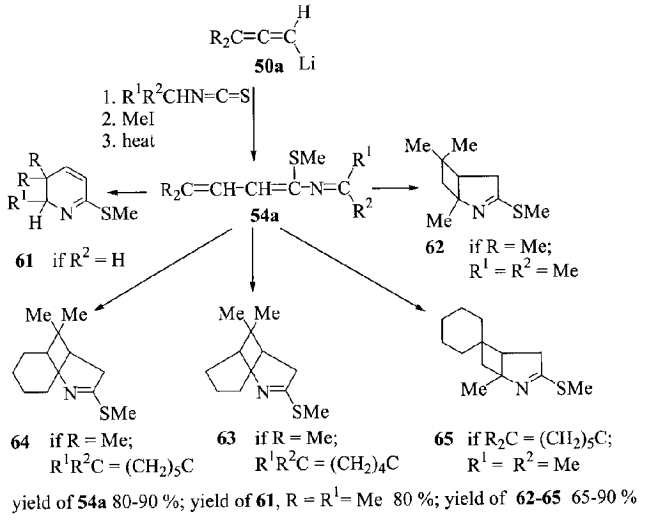
From *t*BuCH=C=CHLi (**48**), MeN=C=S and methyl iodide, 3-*tert*-butyl-6-methylthio-2,3-dihydropyridine (**59**) was obtained. On being heated to reflux at atmospheric pressure, **59** underwent aromatisation with the formation of pyridine **60** (Scheme 16).[31]



Scheme 16. Synthesis of 3-*tert*-butyl-6-methylthio-2,3-dihydropyridine and its aromatisation

V-3. Formation of Cyclobutanopyrrolines

Syntheses with the lithiated, geminally disubstituted allenes R_2C=C=CHLi **50a** (cf. **50** from Scheme 14) and iso-

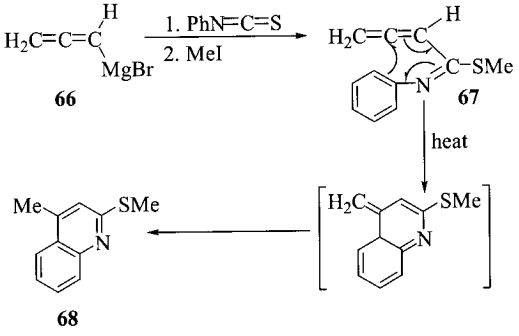


Scheme 17. Formation of 2,3-dihydropyridines or cyclobutanopyrrolines

thiocyanates $R^1R^2CHN{=}C{=}S$ resulted in all cases in the fully conjugated azatrienes $R_2C{=}CHCH{=}C(SMe)N{=}CR^1R^2$ **54a** (cf. **54** in Scheme 15). Heating of the latter at temperatures of at least 220 °C afforded either the expected 2,3-dihydropyridines **61**, or cyclobutanopyrrolines **62**−**65** (Scheme 17), depending on the nature of the substituents R, R^1 and R^2, in good to excellent yields.[33,37] The mechanistic aspects of the formation of **62**−**65** have not yet been investigated, although an attempt to explain their formation has been made.[34]

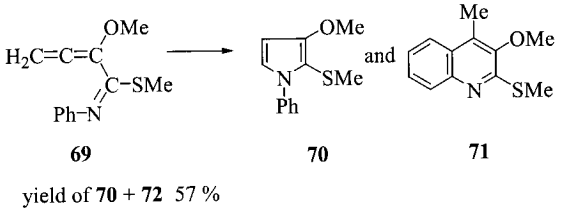
V-4. Formation of Quinolines

German chemists[35] have described the formation of 2-amino-substituted quinolines by cyclisation of the $H_2C{=}C{=}CHC(NR_2){=}N$-aryl system under mild conditions. The thermally induced cyclisation of the thioimidate **67** to quinoline **68** after treatment of **66** (Scheme 18) with phenyl isothiocyanate and subsequent methylation at sulfur[36] is analogous.



Scheme 18. 2-Methylthio-4-methylquinoline from allenylmagnesium bromide and phenyl isothiocyanate

We have isolated a number of quinoline derivatives, all with SMe groups at their 2-positions, in high yields from reactions involving *t*BuCH=C=CHLi, $Me_2C{=}C{=}CHLi$, $(CH_2)_5C{=}C{=}CHLi$ or MeSC(Li)=C=CHLi and aryl isothiocyanates.[37−41] The treatment of methoxyallenyllithium with phenyl isothiocyanate and subsequent methylation exclusively gave the allenic product **69**. Heating of this gave a mixture of equal amounts of the pyrrole **70** and the quinoline **71** (Scheme 19), which could be separated by extraction with dilute acid.[41]

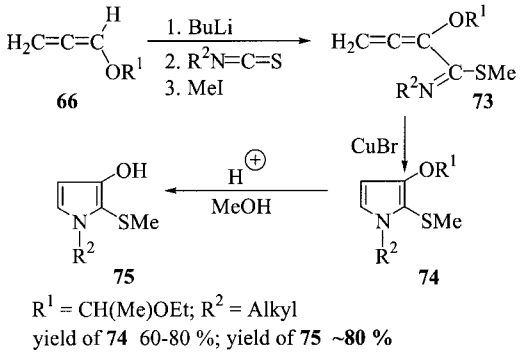


Scheme 19. Formation of pyrroles and quinolines

The addition of lithiated 2-butyne to phenyl isothiocyanate and subsequent methylation gave only about 20% of the product $H_2C{=}C{=}C(CH_3)C(SCH_3){=}NPh$ derived from the reaction of the lithiated acetylene in the allenic form. The other components of the product mixture were $CH_3C{\equiv}CCH_2C(SCH_3){=}NPh$ and $CH_3CH{=}C{=}CH{-}C(SCH_3){=}NPh$, the latter presumably being formed by isomerisation of the acetylenic thioimidate under the weakly basic conditions during the *S*-methylation. After heating at temperatures above 100 °C, a 20:80 mixture of 3,4-dimethyl-2-methylthioquinoline and 4-ethyl-2-methylthio-quinoline was obtained in good combined overall yields. It is assumed that the acetylenic thioimidate isomerises under these conditions to the allenic derivative (probably under the influence of traces of potassium carbonate, the drying agent), which then cyclises to give 4-ethyl-2-methylthioquinoline.[42]

V-5. Copper-Catalysed Synthesis of Pyrrole Derivatives

As mentioned in Section V-2, mixtures of pyrroles and 2,3-dihydropyridines have been obtained by heating the thioimidates formed by addition of lithiated allenic ethers to isothiocyanates and subsequent *S*-methylation. We have found that copper(I) bromide specifically catalyses the cyclisation of **73** to the pyrrole derivatives **74** under mild conditions[43] (Scheme 20). The syntheses are conveniently carried out as one-pot procedures and give good overall yields.



Scheme 20. Synthesis of 3-hydroxypyrroles from allenic ethers and isothiocyanates

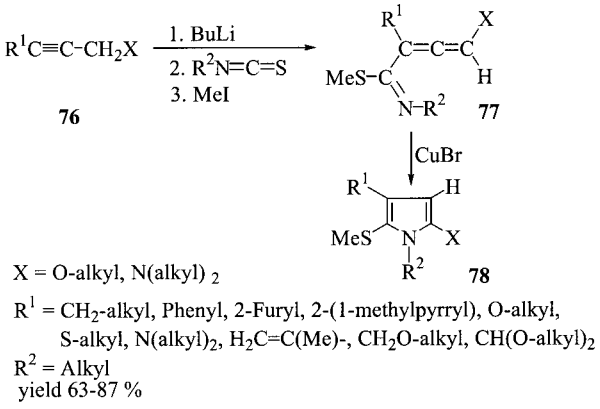
The catalytic action of copper salts may be explained by assuming copper complexation with the allenic system and with nitrogen, thus facilitating the attack of nitrogen at the terminal carbon atom of the allenic system (for copper halide-catalysed reactions between allenic ethers and Grignard reagents see ref.[2a] pp. 184, 185). In a similar manner, pyrrole derivatives with a *tert*-butyl and a methylthio group at their 2- and 5-positions have been obtained from *t*BuCH=C=CHLi and isothiocyanates.[5,24] In these cases it was found to be more convenient to isolate the thioimidates $tBuCH{=}C{=}CHC(SCH_3){=}NR^2$ first and then to heat their concentrated solutions in tetrahydrofuran with CuBr at 60 to 70 °C. For good results in syntheses of *N-aryl*pyrroles it is necessary to suppress the very readily occurring spontaneous cyclisation of the adducts to thiophene derivatives (see Section V-1), by performing the addition of lithiated allenic ethers to aryl isothiocyanates and the subsequent *S*-methylation (preferably with a very large excess of methyl iodide) at temperatures as low as possible. Nevertheless, in some

cases small amounts of 3-methoxy-2-*N*-methyl-2-*N*-arylthiophenes are still formed. We succeeded in removing the aminothiophenes by extracting the mixtures with 30% aqueous hydrochloric acid: surprisingly, the pyrrole derivatives were stable under these conditions.[5,24]

Our copper-catalysed pyrrole synthesis can be applied to the preparation of the little known[44] 3-hydroxypyrroles **75** (Scheme 20), starting with the readily available[24,45] allenic acetal **66** [R^1 = $CH(CH_3)OC_2H_5$]. A few representatives were prepared in good yields by treatment of the pyrroles **74**, obtained by copper-catalysed cyclisation of **73**, with a catalytic amount of hydrochloric acid in methanol.[68]

V-6. Synthesis of 1,2,3,5-Tetrasubstituted Pyrroles

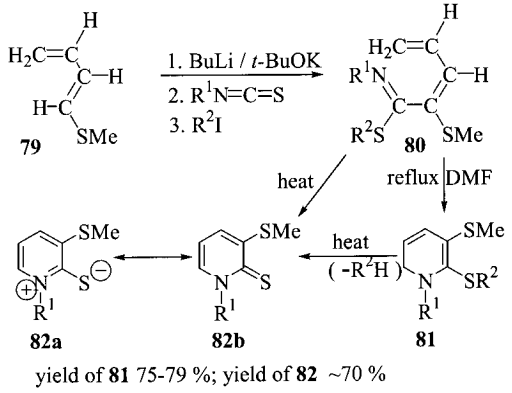
Whereas lithiated 2-alkynylamines and the corresponding lithiated ethers **76** in many cases give mixtures of the α- and γ-substituted compounds in reactions with electrophiles,[46−48] we found that the γ adducts **77** were formed exclusively in reactions with alkyl isothiocyanates and subsequent methylation (Scheme 21). Some of these products underwent spontaneous cyclisation to the tetrasubstituted pyrroles **78** during workup, but small amounts of copper(I) bromide were usually necessary. A wide variety of tetrasubstituted pyrroles was obtained in good overall yields.[49]



Scheme 21. 1,2,3,5-Tetrasubstituted pyrroles from 2-alkynylamines or ethers and alkyl isothiocyanates

VI. Reactions between Heterosubstituted Conjugated Dienes and Isothiocyanates

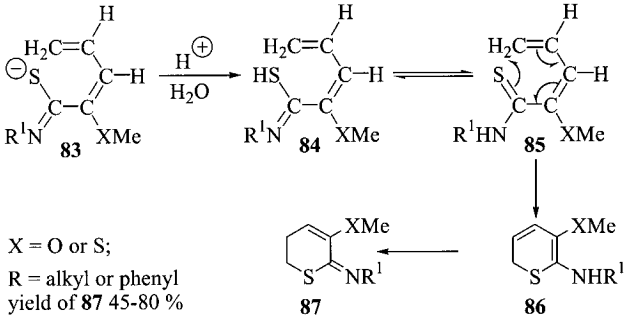
By following the metallation, addition and *S*-alkylation sequence applied in the preceding section, we succeeded in obtaining the azatrienes **80** from the readily available *E* isomer[50] (**79**) of methylthiobutadiene (Scheme 22). As was to be expected from the retained *E* configuration of the internal double bond,[51] the azatrienes underwent cyclisation to the 1,2-dihydropyridines **81** on being heated for short periods in dimethylformamide.[52] Yields were fair to good.



Scheme 22. Synthesis of 1,2-dihydropyridines and their thermal behaviour

If the azatrienes **80** (R^1 = Me, R^2 = Me or Et) were heated in the absence of solvent, the cyclic thioamide **82b** was formed as the main product in fair yields. The driving force for this reaction, in which methane or ethane is eliminated, may be a high contribution from the aromatic structure **82a**.

Treatment of the solutions containing the adducts **83** (from isothiocyanates and the α-metallated dienes) with a calculated amount of acid afforded the iminothiopyrans[53] **87**. Their formation may proceed as shown in Scheme 23.



Scheme 23. 2-Imino-*2H*-thiopyrans from 1-metallated 1,3-butadienes and isothiocyanates

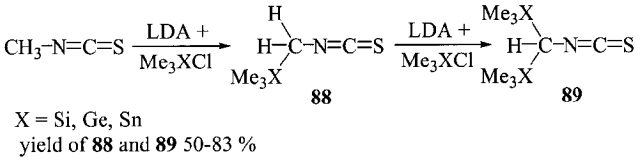
VII. Interactions between Alkyl Isothiocyanates and Alkali Metal Diisopropylamide

In many syntheses, a compound is functionalised by deprotonation with a suitable basic reagent and subsequent addition of an electrophile. For alkyl isothiocyanates, such a procedure is not possible in two separate operations because the anionic species immediately adds to the neutral isothiocyanate molecule, with formation of a cyclic product.

This section deals with the synthetic applications of this reaction between isothiocyanates and strongly basic reagents.

VII-1. In-Situ Trapping of Isothiocyanate Anions

Addition, at very low temperatures, of an ethereal solution of lithium diisopropylamide (LDA) to a 1:1 mixture of equivalent amounts of methyl isothiocyanate and chlorotrimethylsilane gave the silylated isothiocyanate **88** in good yield[54] (Scheme 24). The use of two equivalents of methyl isothiocyanate and the silyl halide enabled a second silyl group to be introduced. The analogous germanium and tin derivatives **88** and **89** were synthesised by similar procedures.[5,24]

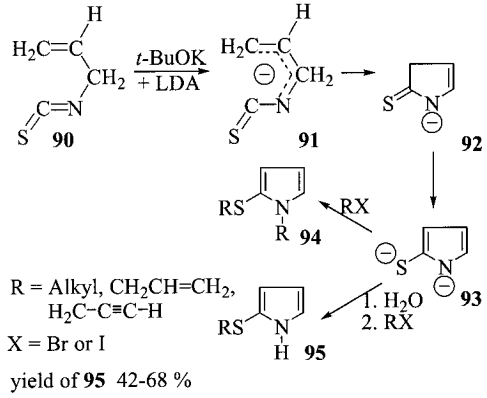


Scheme 24. In situ trapping of lithiated methyl isothiocyanate

Successful silylations, with formation of H_2C=CHCH($SiMe_3$)N=C=S and Me_3SiCH_2CH=C($SiMe_3$)N=C=S or PhCH($SiMe_3$)N=C=S and PhC($SiMe_3$)$_2$N=C=S, respectively, have also been carried out with allyl and benzyl isothiocyanate.[5,24,55] Trapping experiments with the less-acidic ethyl isothiocyanate failed to give the expected derivatives.[5] German chemists[56] carried out in situ trapping experiments with isothiocyanates containing electron-withdrawing groups, such as ROOC, with potassium *tert*-butoxide or sodium hydride as bases and carbonyl compounds as trapping reagents.

VII-2. Cyclisation of the Allyl Isothiocyanate Anion

With the aim of generating the anion **91** from allyl isothiocyanate and to derivatise it with electrophiles in a subsequent step, we added the isothiocyanate to a solution containing a 1:1 molar mixture of LDA and potassium *tert*-butoxide. However, the pyrrole derivatives **94** were obtained upon addition of an excess of a reactive halide. From this result we concluded that the expected anion **91** had indeed formed, but that it had undergone electrocyclisation to give **92**, which had in turn been converted into the dianion **93** in a subsequent deprotonation reaction. This observation resulted in a synthetic route to the 2-(alkylthio)pyrroles[57] **95** (Scheme 25).

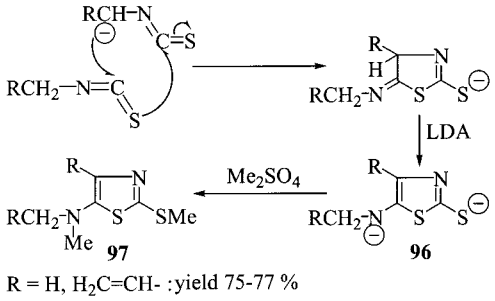


Scheme 25. 2-(Alkylthio)pyrroles from allyl isothiocyanate

When the kinetically less-potent base LDA was used in the treatment with allyl isothiocyanate, the predominant reaction was formation of a thiazole derivative by self-condensation[58] (see below). Yields of the 2-alkylthiopyrroles, which were fair in the case of LDA-*t*BuOK, were increased by about 10% if caesium *tert*-amylate was used instead of *t*BuOK.[5]

VII-3. Dimeric and Trimeric Condensation Reactions

The addition of methyl isothiocyanate to a strongly cooled solution of two mol equivalents of LDA in tetrahydrofuran, followed by treatment with dimethyl sulfate at somewhat higher temperatures, gave the thiazole derivative **97** (R = H) in high yield (Scheme 26).[59–66] Analogous products were obtained from allyl-[58] and benzyl isothiocyanate.[5]



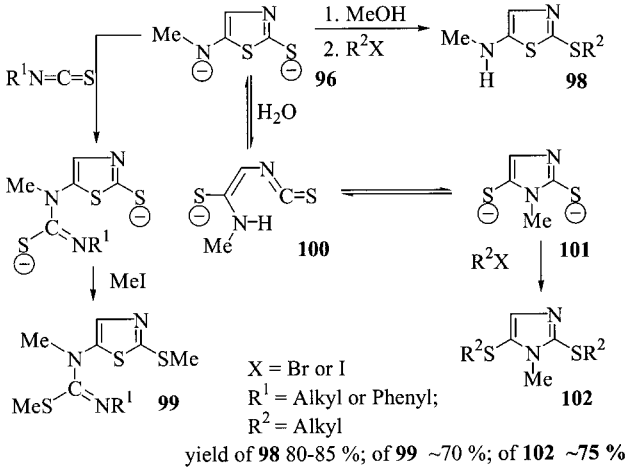
Scheme 26. Base-induced self-condensation of methyl and allyl isothiocyanate

From the solution of the condensation product **96** (R = H), some other products were obtained, also in good yields (Scheme 27). Addition at −20 °C of a slight excess of methanol, followed by *S*-alkylation, gave the *N*-monosubstituted thiazoles **98** (cf ref.[67]). A further quantity of methyl isothiocyanate reacted specifically with the most strongly basic centre in **96**, and subsequent methylation afforded the "trimeric" condensation product **99**. A similar result was obtained with phenyl isothiocyanate (R^1 = Ph).[5,24] Treatment of the solution of dianion **96** with water at room temperature, followed by methylation, gave the imidazole derivative **102**. This surprising result may be explained by assuming an equilibrium between **96** and the ring-opened intermediate **100**, which re-closes to **101**.[59]

Similar condensation reactions attempted with ethyl isothiocyanate and LDA were unsuccessful (the predominant reaction was addition of LDA), but promising results were obtained with the kinetically stronger 1:1 molar combination of LDA and *t*BuOK.[5]

Concluding Remarks

The products formed by the addition of alkali metal derivatives of unsaturated compounds to isothiocyanates or non-enethiolisable dithioesters and by treatment of isothiocyanates with strongly basic reagents can be converted into heterocyclic compounds. Depending upon the nature



Scheme 27. Various transformations with the condensation product of methyl isothiocyanate

of the subsequent reactions undertaken with these initial products and the order in which they are performed, a wide variety of heterosubstituted (amino, ether or thioether groups) heterocycles are obtainable in satisfactory yields. As the synthesised compounds are impossible or more difficult to prepare otherwise, the various routes to the heterocyclic compounds constitute fundamentally new approaches.

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[1] L. Lochmann, *Eur. J. Inorg. Chem.* **2000**, 1115−1126.
[2] [2a] L. Brandsma, H. D. Verkruijsse, *Synthesis of Acetylenes, Allenes and Cumulenes*, Elsevier, Amsterdam 1981. – [2b] L. Brandsma, H. D. Verkruijsse, *Preparative Polar Organometallic Chemistry*, Springer Verlag, Heidelberg, **1987**, Vol. 1; **1991**, Vol. 2. – [2c] L. Brandsma, *Preparative Acetylenic Chemistry*, 2nd ed., Elsevier, Amsterdam, **1988**.
[3] R. Epsztein, in *Comprehensive Carbanion Chemistry*, Part B, (Eds.: E. Buncel, T. Durst), Elsevier, Amsterdam, **1984**, pp. 107−175.
[4] B. J. Wakefield, *Organolithium Methods*, Academic Press, London, **1988**, pp. 96, 102; K. A. Petrov, L. N. Andreev, *Usp. Khim.* **1969**, *38*, 41−72; M. S. Kharash, O. Reinmuth, in *Grignard Reactions of Nonmetallic Substances*, Prentice Hall, New York, **1954**, Chapter 19, pp. 1199−1204; N. A. LeBel, R. M. Cherluck, E. A. Custin, *Synthesis* **1973**, 678−679; D. A. Shirley, M. D. Cameron, *J. Am. Chem. Soc.* **1972**, *72*, 664−665; J. J. Fitt, H. W. Gschwend, *J. Org. Chem.* **1979**, *44*, 303−305; P. Gosselin, S. Masson, A. Thuiller, *Tetrahedron Lett.* **1978**, 2715−216.
[5] Unpublished results from the author's laboratory.
[6] L. Brandsma, N. A. Nedolya, V. P. Zinov'eva, G. I. Sarapulova, B. A. Trofimov, *Russ. J. Org. Chem.* **1999**, *35*, 216−224.
[7] Y. A. Heus-Kloos, R. L. P. de Jong, H. D. Verkruijsse, L. Brandsma, S. Julia, *Synthesis* **1985**, 958−959.
[8] O. A. Tarasova, L. V. Klyba, V. Yu. Vvedensky, N. A. Nedolya, B. A. Trofimov, L. Brandsma, H. D. Verkruijsse, *Eur. J. Org. Chem.* **1998**, 253−256.
[9] O. A. Tarasova, N. A. Nedolya, V. Yu. Vvedensky, L. Brandsma, B. A. Trofimov, *Tetrahedron Lett.* **1997**, *38*, 7241−7242.
[10] G. R. Khan, K. A. Povev, F. Scheinmann, *J. Chem. Soc., Chem. Commun.* **1979**, 215−216.
[11] H. Hommes, H. D. Verkruijsse, L. Brandsma, *Recl. Trav. Chim.* **1980**, *99*, 113−114; L. Brandsma, E. Mugge, *Recl. Trav. Chim.* **1973**, *92*, 628−630.
[12] R. L. P. de Jong, H. D. Verkruijsse, L. Brandsma, in *Perspectives in the Organic Chemistry of Sulfur* (Eds.: B. Zwanenburg, A. J. H. Klunder), Elsevier, Amsterdam, **1987**, pp. 105−117.
[13] R. L. P. de Jong, L. Brandsma, *Synth. Commun.* **1990**, *20*, 3427−3431.
[14] L. Brandsma, B. A. Trofimov, O. A. Tarasova, N. A. Nedolya, A. L. Spek, A. V. Afonin, S. V. Zinchenko, *Tetrahedron Lett.* **2001**, *42*, 4687−4689.
[15] N. A. Nedolya, L. Brandsma, B. A. Trofimov, *Russ. J. Org. Chem.* **1997**, *33*, 557−558.
[16] H. Westmijze, K. Ruitenberg, J. Meijer, P. Vermeer, *Tetrahedron Lett.* **1980**, *21*, 1771−1775; H. Westmijze, K. Ruitenberg, J. Meijer, P. Vermeer, *Synthesis* **1981**, 551−553.
[17] R. L. P. de Jong, L. Brandsma, *J. Organomet. Chem.* **1982**, *238*, C17−C20.
[18] R. L. P. de Jong, L. Brandsma, *Synth. Commun.* **1991**, *21*, 145−149.
[19] R. L. P. de Jong, L. Brandsma, *J. Chem. Soc., Chem. Commun.* **1983**, 1056−1057; R. L. P. de Jong, Dissertation. Utrecht, **1990**.
[20] R. L. P. de Jong, L. Brandsma, *J. Organomet. Chem.* **1986**, *312*, 277−282.
[21] S. Masson, M. Saquet, A. Thuiller, *Tetrahedron* **1977**, *33*, 2949−2953.
[22] D. Paquer, M. Vazeux, *J. Organomet. Chem.* **1977**, *140*, 257−264.
[23] R. L. P de Jong, L. Brandsma, *J. Organomet. Chem.* **1986**, *316*, C21−C23.
[24] N. A. Nedolya, Dissertation, Utrecht, May **1999**.
[25] L. Brandsma, N. A. Nedolya, O. A. Tarasova, L. V. Klyba, L. M. Sinegovskaya, B. A. Trofimov, *Dokl. Akad. Nauk* **1997**, *357*, 350−351; L. Brandsma, O. A. Tarasova, V. Yu Vvedensky, R. L. P. de Jong, L. V. Klyba, H. D. Verkruijsse, N. A. Nedolya, B. A. Trofimov, *Russ. J. Org. Chem.* **1999**, *35*, 1228−1233.
[26] L. Brandsma, V. Yu. Vvedensky, N. A. Nedolya, O. A. Tarasova, B. A. Trofimov, *Tetrahedron Lett.* **1998**, *39*, 2433−2436.
[27] A. I. Meyers, J. J. Ritter, *J. Org. Chem.* **1958**, *23*, 1918−1922.
[28] A. I. Meyers, J. Schneller, N. K. Ralhan, *J. Org. Chem.* **1963**, *28*, 2944−2950.
[29] A. I. Meyers, B. J. Betrus, N. K. Ralhan, K. B. Rao, *J. Heterocycl. Chem.* **1964**, *1*, 13−18.
[30] R. Fuks, R. Merenyi, H. G. Viehe, *Bull. Soc. Chim. Belg.* **1976**, *83*, 147−149.
[31] N. A. Nedolya, L. Brandsma, R.-J. De Lang, B. A. Trofimov, *Russ. J. Org. Chem.* **1997**, *33*, 580−581.
[32] N. A. Nedolya, L. Brandsma, B. A. Trofimov, *Dokl. Akad. Nauk* **1996**, *350*, 68−69; *Khim. Geterotsikl. Soedin.***1996**, *7*, 917−918; *Zh. Obshch. Khim.* **1996**, *66*, 2042−2043; N. A. Nedolya, L. Brandsma, V. P. Zinov'eva, B. A. Trofimov, *Russ. J. Org. Chem.* **1997**, *33*, 80−85; N. A. Nedolya, L. Brandsma, B. A. Trofimov, *Izv. Akad. Nauk, Ser. Khim.* **1996**, 2813−2814; *Russ. Chem. Bull.* **1996**, *45*, 2670−2671.
[33] L. Brandsma, N. A. Nedolya, W. Heerma, A. C. H. T. M. van der Kerk, E. T. H. G. Lutz, R.-J. de Lang, A. V. Afonin, B. A. Trofimov, *Russ. J. Heterocycl Comp.* **1997**, 493−495; *Russ. Chem. Bull.* **1997**, *46*, 832−833.
[34] B. A. Trofimov, N. A. Nedolya, L. Brandsma, Yu. L. Frolov, E. Yu. Larionova, D.-S. D. Toryashinova, V. B. Kubychev, N. M. Vitkovskaya, *Sulfur Lett.* **1999**, *22*, 249−256.
[35] W. Ried, P. Weidemann, *Chem. Ber.* **1971**, *104*, 3329−3340.
[36] G. Darnault, M. Saquet, A. Thuiller, *Chem. Ind.* (London), no. 10, **1983**, 391−392.

[37] L. Brandsma, N. A. Nedolya, H. D. Verkruijsse, N. L. Owen, Du Li, B. A. Trofimov, *Tetrahedron Lett.* **1997**, *38*, 6905−6908.
[38] L. Brandsma, N. A. Nedolya, R.-J. de Lang, B. A. Trofimov, *Russ. Chem. Bull.* **1996**, *45*, 2873−2874.
[39] L. Brandsma, N. A. Nedolya, R.-J. de Lang, B. A. Trofimov, *Russ. J. Heterocycl. Comp.* **1997**, *33*, 491−492.
[40] N. A. Nedolya, L. Brandsma, R.-J. de Lang, B. A. Trofimov, *Russ. J. Org. Chem.* **1997**, *33*, 1361−1362.
[41] L. Brandsma, N. A. Nedolya, O. A. Tarasova, L. V. Klyba, L. M. Sinegovskaya, B. A. Trofimov, *Russ. J. Org. Chem.* **1999**, *35*, 928−1932.
[42] F. Taherirastgar, N. A. Nedolya., L. Brandsma, R.-J. de Lang, B. A. Trofimov, *Dokl. Akad. Nauk* **1997**, *353*, 64−65.
[43] N. A. Nedolya, L. Brandsma, O. A. Tarasova, H. D. Verkruijsse, B. A. Trofimov, *Tetrahedron Lett.* **1998**, *39*, 2409−2410.
[44] H. McNab, L. C. Monahan, in *The Synthesis, Reactivity and Physical Properties of Substituted Pyrroles*, Part 2 in the series *The Chemistry of Heterocyclic Compounds.* A Series of Monographs (Ed.: E. C. Taylor), John Wiley, New York, **1992**, pp. 525−616.
[45] S. Hoff, L. Brandsma, J. F. Arens, *Recl. Trav. Chim.* **1968**, *87*, 1179−1184.
[46] E. J. Corey, S. Terashima, *Tetrahedron Lett.* **1972**, 1815−1816.
[47] F. Mercier, R. Epsztein, S. Holland, *Bull. Soc. Chim. Fr.* **1972**, 690−696.
[48] R. Epsztein, F. Mercier, *Synthesis* **1977**, 183−184.
[49] L. Brandsma, N. A. Nedolya, B. A. Trofimov, *Eur. J. Org. Chem.* **1999**, 2663−2664.
[50] R. H. Everhardus, A. Peterse, P. Vermeer, L. Brandsma, J. F. Arens, *Recl. Trav. Chim., Pays-Bas* **1974**, *93*, 90−91.
[51] R. H. Everhardus, R. Gräfing, L. Brandsma, *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 69−72.
[52] N. A. Nedolya, L. Brandsma, A. H. T. M. van der Kerk, V. Yu. Vvedensky, B. A. Trofimov, *Tetrahedron Lett.* **1998**, *39*, 1995−1996; N. A. Nedolya, L. Brandsma, H. D. Verkruijsse, A. C. H. T. M. van der Kerk, B. A. Trofimov, *Dokl. Akad. Nauk* **1998**, *360*, 356−359.
[53] N. A. Nedolya, L. Brandsma, H. D. Verkruijsse, A. H. T. M. van der Kerk, B. A. Trofimov, *Tetrahedron Lett.* **1998**, *39*, 2631−2634; N. A. Nedolya, L. Brandsma, H. D. Verkruijsse, B. A. Trofimov, *Russ. J. Heterocycl. Chem.* **1998**, 550−553.
[54] L. Brandsma, N. A. Nedolya, H. D. Verkruijsse, B. A. Trofimov, *Synthesis* **1997**, 423−424.
[55] L. Brandsma, N. A. Nedolya, B. A. Trofimov, *Mendeleev Commun.* **1997**, 232−233.
[56] D. Hoppe, R. Follmann, *Chem. Ber.* **1976**, *109*, 3047−3061.
[57] N. A. Nedolya, L. Brandsma, B. A. Trofimov, *Russ J. Org. Chem.* **1998**, *34*, 900−901; L. Brandsma, N. A. Nedolya, B. A. Trofimov, *Dokl. Akad. Nauk* **1998**, *358*, 196−197; N. A. Nedolya, L. Brandsma, H. D. Verkruijsse, B. A. Trofimov, *Tetrahedron Lett.* **1997**, *38*, 7247−7248; L. V. Klyba, V. N. Bochkarev, L. Brandsma, N. A. Nedolya, B. A. Trofimov, *Russ. J. Gen. Chem.* **1999**, *69*, 1805−1808.
[58] N. A. Nedolya, L. Brandsma, A. C. H. T. M. van der Kerk, A. V. Afonin, R.-J. de Lang, B. A. Trofimov, *Russ. J. Org. Chem.* **1998**, *34*, 680−684.
[59] N. A. Nedolya, L. Brandsma, B. A. Trofimov, *Tetrahedron Lett.* **1997**, *38*, 6279−6280; L. Brandsma, N. A. Nedolya, H. D. Verkruijsse, B. A. Trofimov, *Russ. J. Chem. Heterocycl. Comp.* **1997**, *33*, 1118−1120.
[60] L. Brandsma, N. A. Nedolya, H. D. Verkruijsse, B. A. Trofimov, *Khim. Geterotsikl. Soedin.* **1997**, 1275−1277.
[61] L. Brandsma, N. A. Nedolya, B. A. Trofimov, *Russ. Chem. Bull.* **1998**, *47*, 187−188.
[62] N. A. Nedolya, L. Brandsma, B. A. Trofimov, *Dokl. Akad. Nauk* **1998**, *358*, 72−73.
[63] L. Brandsma, N. A. Nedolya, B. A. Trofimov, *Izv. Akad. Nauk, Ser. Khim.* **1998**, 541−542; *Russ. Chem. Bull.* **1998**, 523−524.
[64] N. A. Nedolya, L. Brandsma, A. C. H. T. M. van der Kerk, A. V. Afonin, R.-J. de Lang, B. A. Trofimov, *Zh. Org. Khim.* **1998**, *34*, 722−726.
[65] N. A. Nedolya, L. Brandsma, A. C. H. T. M. van der Kerk, H. D. Verkruijsse, G. I. Sarapulova, A. V. Afonin, B. A. Trofimov, *Russ. J. Org. Chem.* **1999**, *35*, 921−927.
[66] N. A. Nedolya, L. Brandsma, A. C. H. T. M. van der Kerk, A. V. Afonin, R.-J. de Lang, B. A. Trofimov, *Russ. J. Gen. Chem.* **1997**, *67*, 656−657.
[67] I. Hoppe, D. Hoppe, U. Schöllkopf, *Tetrahedron Lett.* **1976**, 609−612.
[68] L. Brandsma, N. A. Nedolya, B. A. Trofimov, *Russ. Chem. Bull.* **2000**, 1634−1636.

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