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Reactions of Cycloaliphatic Thioketones and Their Oxo Analogues with Lithiated Methoxyallene: A New Approach to Vinylthiiranes

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In memory of Professor Roland Mayer (Dresden), one of the pioneers of modern organosulfur chemistry

Abstract: Admantanethione smoothly reacted with lithiated methoxyallene at low temperatures yielding the expected allenyl-substituted thiolate, which upon aqueous work-up underwent spontaneous 1,3-cyclization to afford a hitherto unknown methoxy-substituted vinylthiirane derivative. The analogous reaction with adamantanone led to the corresponding allenyl alcohol that can be isolated and—depending on the conditions applied—either be converted into the corresponding vinyloxirane or into the 2,5-dihydrofuran derivative. Sterically more crowded thioketones were also combined with lithiated methoxyallene, but in these cases competitive 1,5-cyclization leading to isomeric dihydrothiophene derivatives was observed. DFT calculations of model intermediates and products show distinct energy differences of the sulfur and the corresponding oxygen compounds. Desulfurization of the adamantanethione-derived vinylthiirane yielded a methoxy-substituted 1,3-diene that was studied in cycloadditions with electron-deficient dienophiles. Whereas in the case of tetracyanoethylene the corresponding cyclobutane derivative was formed, the reaction with nitrosobenzene provided the expected 1,2-oxazine derivative. By reductive cleavage of the N–O bond this heterocycle was converted into an unsaturated amino alcohol bearing an adamantane moiety.

Keywords: alkoxyallenes · desulfurization · thiiranes · thioketones · thiophenes

Introduction

Additions of organolithium compounds to aldehydes and ketones belong to the standard methods in organic synthesis and are widely applied for the preparation of secondary and tertiary alcohols. Reactions of that type occur as ionic or single-electron transfer processes and, to the best of our knowledge, all additions proceed selectively by carbophilic attack to the carbonyl group.[1] On the other hand, the sulfur analogues, that is, thioaldehydes and thioketones, were only scarcely used as starting materials in reactions with organometallic compounds. Moreover, due to the instability of thioaldehydes, they are applied in organic synthesis to a very limited extent.[2] Thioketones are more useful and especially the non-enolizable cycloaliphatic representatives are considered as an attractive class of substrates for studies focused on the reactivity of the C=S group.[3]

One of the most remarkable features of thioketones is their excellent reactivity as dipolarophiles observed in [3+2] cycloadditions with 1,3-dipoles such as diazoalkanes,[4a] nitrones,[4b,c] thiocarbonyl *S*-sulfides (thiosulfines),[4d,e] and thiocarbonyl ylides.[4e] These cycloadditions open a convenient access to diverse five-membered sulfur heterocycles.[5] Due to the extremely high reactivity displayed towards 1,3-dipoles, in particular with diazoalkanes and thiocarbonyl ylides, thioketones were called super-dipolarophiles.[5b] It is well known that the electronegativity values of carbon and sulfur atoms are equal according to the Pauling scale and, therefore, the C=S bond is essentially unpolarized.[6] Although the reactions of thioketones with organometallic compounds were reported in the literature, the reaction course and the type of the products formed differ significantly, depending on the nature of the solvent and the reaction partners used. Adamantanethione **1a** is most often applied as a model thioketone for the reactions with organometallics. The reactions of **1a** with Grignard reagents yield mainly products of thiophilic attack of the nucleophilic species; however, the competitive carbophilic approach as a result of a solvent effect was also observed (Scheme 1).[7] On the other hand, in certain cases allylic organometallic reagents are reported to form initially products of carbophilic

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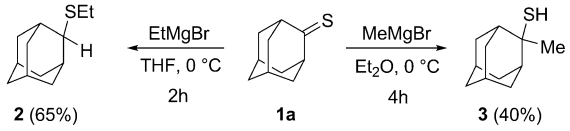
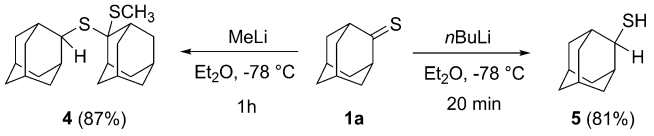


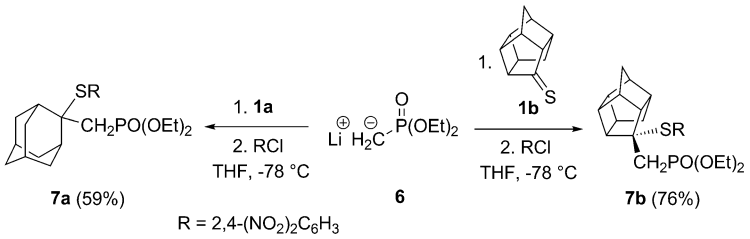
Scheme 1. Thiophilic versus carbophilic attack observed for additions of Grignard reagents to adamantanethione **1a**.



Scheme 2. Reactions of **1a** with alkyllithiums.

attack, which subsequently undergo a [2,3]-sigmatropic rearrangement, yielding the S-adducts as final products.[8]

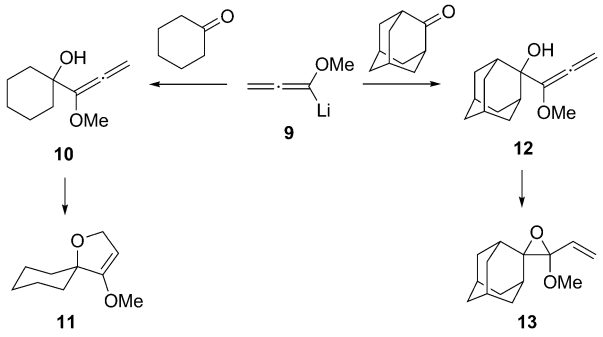
In recent publications, reactions of **1a** with a series of alkyllithiums were described. Whereas the reaction with methyllithium provided bisthioether **4** as the main product, the analogous transformation with *n*-butyllithium yielded adamanthane-2-thiol **5** as the major component (Scheme 2).[9] The formation of **4** is explained by an initial thiophilic attack of methyllithium, followed by the reaction with a second molecule of **1a**. By contrast, the mechanistic explanation for the formation of thiol **5** is based on the known ability of compounds such as *n*BuLi for hydride transfer onto C=X bonds (X = S, O).[1b,10] These results are supported by computations suggesting that alkyllithium agents tend to react with **1a** by an initial thiophilic attack.



Scheme 3. Selective carbophilic addition of lithiated methylphosphonate **6** onto thioketones **1a** and **1b**.

Addition of lithiated methylphosphonate **6** to cycloaliphatic thioketones **1a** and **1b** furnished products **7a** and **7b**, respectively, as a result of carbophilic attack (Scheme 3). The intermediate thiolate anions were trapped in both examples with 1-chloro-2,4-dinitrobenzene to give the corresponding thioethers.[11] Similarly, additions of carbanions, generated from esters and nitriles by treatment with lithium diisopropylamide, to the C=S bond of **1a** results in the exclusive formation of thiol derivatives as the products of reactions with the thioketone carbon atom.[12] Apparently, carbanions stabilized by electron-withdrawing substituents such as enolates strongly prefer the carbophilic attack.

Lithiated methoxyallene **9** is known as a versatile nucleophilic C3 building block that has found numerous applications in the synthesis of diverse functionalized heterocycles by its additions to electrophiles such as carbonyl compounds, imines, nitriles, and nitrones.[13] The additions of **9** to aliphatic aldehydes and ketones typically lead to primary adducts (**10** and **12**) that can be cyclized under basic conditions or by Lewis acid catalysis to form 2,5-dihydrofuran derivatives such as **11** (Scheme 4).[14] However, in rare cases



Scheme 4. Addition of lithiated methoxyallene **9** to cycloaliphatic ketones and competing 1,5- and 1,3-cyclizations of primary adducts **10** and **12** to dihydrofuran **11** and vinyloxirane **13**.

Abstract in Polish: Adamantantion łatwo reaguje z litowanym metoksyallenem w niskich temperaturach prowadząc do oczekiwanego allenylotiolanu, który podczas obróbki wodnej ulega spontanicznej cyklizacji-1,3 do dotychczas nieznanej pochodnej metoksy-winylotiiranu. W analogicznej reakcji z użyciem adamantanonu wyizolowano pośredni allenyloalkohol, który w zależności od warunków reakcji ulega cyklizacji do odpowiedniej pochodnej winylooksiranu lub do 2,5-dihydrofuranu. Sterycznie zatłoczone tioketony również reagowały z metoksyallenylolitem, jednak w tych przypadkach dominowała cyklizacja-1,5 prowadząca do izomerycznych pochodnych dihydrotiofenu. Obliczenia DFT modelowych związków przejściowych oraz produktów wykazały znaczące różnice energii pomiędzy pochodnymi siarkowymi a ich analogami tlenowymi. Desulfuracja winylotiiranu pochodnego adamantantionu prowadzi do metoksy-1,3-dienu, który przetestowano w reakcjach cykloaddycji wobec zubożonych elektronowo dienofili. W przypadku reakcji z tetracyjanoetylenem otrzymano odpowiednią pochodną cyklobutanu, podczas gdy w reakcji z nitrozobenzenem, zgodnie z oczekiwaniem, uzyskano pochodną 1,2-oksazyny. Reduktywne otwarcie wiązania N–O tego heterocykla umożliwiło syntezę nienasyconego aminoalkoholu sfunkcjonalizowanego grupą adamantylową.

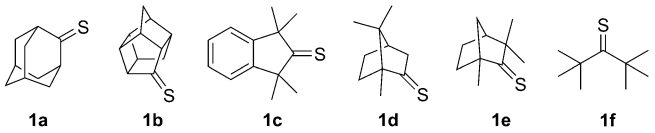


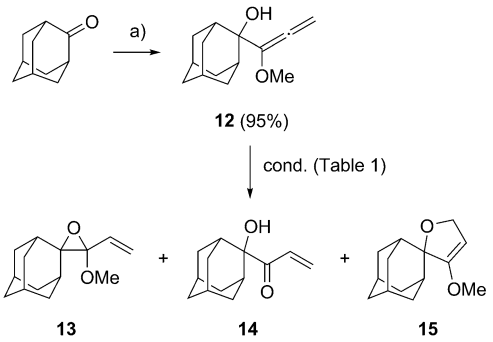
Figure 1. Thioketones **1a–1f** selected for the study towards lithiated methoxyallene **9**.

the competitive formation of the isomeric vinyloxiranes of type **13** as products of a 1,3-cyclization was also noticed.[14b]

Due to our ongoing interest in the use of thiocarbonyl compounds for the synthesis of sulfur-containing heterocycles,[15] cycloaliphatic thioketones **1a–f** (Figure 1) were selected as electrophiles and studied in reactions with lithiated alkoxyallenes. The goal of the present study was to gain more insight into the reaction course of thioketones **1** with organolithium compounds such as **9**. Because these are at the borderline of stabilized or unstabilized organometallics, it was particularly interesting to see whether they behave as carbophilic or as thiophilic nucleophiles. In addition, a comparison of the observed results with those obtained with model compound adamantan-2-one should be established.

Results and Discussion

Initial experiments were carried out using adamantanone, which was selected as a sterically crowded model ketone. As expected, slow addition of the ketone to in situ-generated lithiated methoxyallene **9** in THF at −78 °C provided the corresponding allenyl alcohol **12** after aqueous workup as a single product in an excellent yield of 95 %.[14b] Although this compound was stable in the solid state, it slowly converts into vinyloxirane **13** in a [D_6]acetone solution. After seven days, a complete cyclization to **13** was observed, along with traces of enone **14** that is generated by hydrolysis of **12**.[16] Remarkably, the ^{1}H NMR spectrum of **12** recorded in $CDCl_3$ solution showed a more rapid cyclization of the sample (ca. 1:1 ratio of **12**/**13** after 24 h), very likely accelerated by residual DCl of the solvent. After three days, vinyloxirane derivative **13** was found as an exclusive product in this NMR experiment (Scheme 5). The 1,3-cyclizations of allenyl alcohols leading to vinyloxiranes are unique, and to the best of our knowledge, similar reaction outcomes were only observed by Magnus et al. for a few cycloaliphatic derivatives under strongly basic conditions using KO*t*Bu in DMSO.[14b] Moreover, the reactions were reported to occur in a completely selective manner leading to either vinyloxirane or 2,5-dihydrofuran derivatives in high yields. For example, cyclohexanone-derived allenyl alcohol **10** furnished solely 2,5-dihydrofuran **11** (90 %), and adamantane derivative **12** was reported to give oxirane **13** in 92 % yield (see Scheme 4). On the other hand, more recent Au^I/pyridine-catalyzed transformations of allenyl alcohols have been presented as an often superior method in terms of the exclusive formation of 2,5-dihydrofurans.[14d–f] Prompted by these reports, a series of experiments were carried out using freshly prepared primary product **12**. Firstly, *t*BuOK was used as catalyst; however, in our hands in all attempts mixtures of **13** and **15** were found in the crude reaction mixture in an approximate ratio of 1:2 (Scheme 5, Table 1). On the other hand, the Au^I-catalyzed cyclization of **12** yielded the expected 5-membered derivative **15** in good yield (70 %), although vinyloxirane **13** (17 %) was still present in the mixture. In order to test whether **13** can be converted into **15**, the crude mixture was resubmitted under the applied reaction conditions, but no changes in the tested sample could be observed after 3 days. Neither attempted purification by short-path distillation nor chromatography on neutral alumina led to the isolation of pure **15**. Instead, its complete decomposition was noticed in all performed experiments. The observed competitive formation of **13** clearly confirms the high tendency of **12** for the spontaneous 1,3-cyclization, noticed for the pure samples of **12**.



Scheme 5. Synthesis of allenyl alcohol **12** and its subsequent conversion into vinyloxirane **13**, enone **14**, and/or 2,5-dihydrofuran **15**: a) lithiated methoxyallene **9** (1.5 equiv), THF, −78 °C, 30 min, then H_2O.

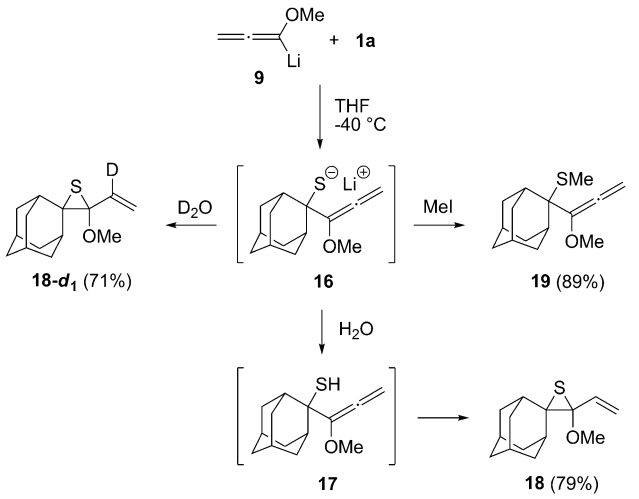
Table 1. Conversions of **12** into **13**, **14**, and **15** under various conditions.

Conditions	**13** [%]	**14** [%]	**15** [%]
[D_6]acetone, 7 d, rt[a]	90	10	–
$CDCl_3$, 3 d, rt[a]	97	3	–
*t*BuOK/DMSO,[b] 1 h, 50 °C	24	–	40
AuCl/Py,[c] CH_2Cl_2, 3 h, rt	17	–	70

[a] NMR experiment. [b] *t*BuOK (0.5 equiv), DMSO (5.0 mL mmol^{-1} of **12**); yields refer to the content of the compound in a purified mixture. [c] AuCl (0.05 equiv), pyridine (0.15 equiv); yields refer to the content of the compound in a purified mixture.

Based on these remarkable observations with adamantanone, we then focused our attention on adamantanethione **1a**. In a typical experiment its solution in dry THF was added at −78 °C to lithiated methoxyallene **9** (1.5–3.0 equiv in THF). The resulting mixture was then quenched with H_2O, and after warming to room temperature, the work-up was performed in a typical manner. After analysis of the crude product mixture by mass spectrometry and ^{1}H NMR spectroscopy, the subsequent purification by column chromatography yielded a sticky colorless oil. The ^{1}H NMR

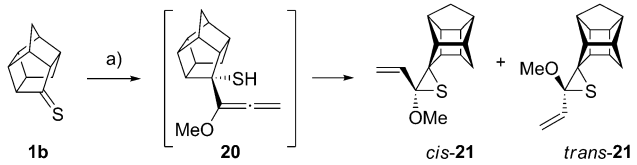
spectrum showed the presence of a diagnostic set of signals located at 5.43 (dd, $J=1.7$, 10.4 Hz), 5.55 (dd, $J=1.7$, 16.8 Hz), and 6.00 (dd, $J=10.4$, 16.8 Hz) ppm, typical for a vinyl moiety. In addition, apart from the group of signals attributed to the adamantane skeleton, the singlet found at 3.43 ppm evidenced the presence of the methoxy substituent. The recorded ^{13}C NMR spectrum confirmed the presence of the vinyl group and showed two additional signals of quaternary carbon atoms at 68.3 and 95.2 ppm. The CI-MS spectrum supported by the elemental analysis confirmed the molecular formula as $C_{14}H_{20}OS$. Based on these data, the structure of the isolated product was elucidated as the spirothiirane derivative **18** (Scheme 6). An attempted isolation of the postulated intermediate allenyl thiol **17** was not successful, in contrast to the above described alcohol **12**. Even in the crude product mixture only signals of **18** but no signals characteristic for compounds of type **17** could be detected. Further optimization of the reaction conditions by the use of higher excess of lithiated methoxyallene **9** (6.0 equiv) at elevated temperature (−40 °C) enabled complete conversion of the starting material and furnished **18** in a high yield of 79%. The isolated product was stable both in the solution and during storage in the refrigerator. However, upon storage in an open flask at room temperature at daylight, compound **18** underwent slow decomposition accompanied by extrusion of elemental sulfur. An attempted Au^I-catalyzed ring expansion of vinylthiirane **18** to the corresponding dihydrothiophene derivative was unsuccessful.



Scheme 6. Addition of lithiated methoxyallene **9** to thioketone **1a** resulting in vinylthiirane derivative **18** or **18-d_1**, respectively, and trapping of intermediate **16** with methyl iodide, furnishing thioether **19**.

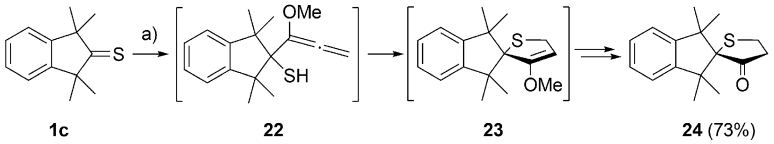
In order to gain more insight into the reaction course, we used methyl iodide to trap the assumed thiolate intermediate **16** (Scheme 6). The crude product obtained after evaporation of the solvent was purified by recrystallization from pentane at low temperatures. Attempted purification by chromatography on silica gel was unsuccessful and led to decomposition of the material. The solid methylation product showed two singlet signals in the ^1H NMR spectrum at 3.45 and 1.87 ppm, respectively, which were attributed to the OMe and SMe groups. In addition, the presence of another singlet at 5.56 ppm (2H) proved the open-chain structure of **19** with an allenyl group. In extension of the investigation, D_2O (instead of H_2O) was used as an electrophile to quench the initially obtained reaction mixture. After separation, the d_1-labelled vinylthiirane **18-d_1** was obtained as a single product. The NMR data confirmed the location of deuterium at C-1' of the vinyl moiety. Based on the collected results, it is plausible to postulate that lithiated methoxyallene **9** undergoes exclusive carbophilic addition onto the C=S group and that the initially formed thiolate **16** is either protonated (by H_2O or D_2O) or alkylated at the sulfur. The intermediate thiol **17** undergoes spontaneous 1,3-cyclization—facilitated presumably by the enhanced acidity of the SH group—to yield vinylthiirane **18**.

As the next model compound we studied the reactions of "cage thioketone" **1b** with lithiated methoxyallene **9**. The reaction was carried out in analogous manner, and the ^1H NMR spectroscopic analysis of the crude product showed the presence of two diastereomeric thiiranes in which the signals of two methoxy groups were found at 3.40 and 3.38 ppm (ratio 61:39). It is known that nucleophiles attack the C=S or C=O unit of Cookson's "birdcage" compounds exclusively from the *exo*-face.[11,17] Therefore, the two isomers are generated during the 1,3-cyclization of the intermediate thiol **20**, affording the mixture of *cis*-**21** and *trans*-**21** in 71% combined yield (Scheme 7). Attempted separation led to isolation of a small sample of the major isomer as an oil; however, an unequivocal assignment of the configuration of the two isomers was not possible.



Scheme 7. Reaction of lithiated methoxyallene **9** with "cage thione" **1b**: a) lithiated methoxyallene **9** (3.0 equiv), THF, −78 °C, 15 min, then H_2O.

Another non-enolizable thioketone, which is frequently used in studies of C=S-containing substrates, is 1,1,3,3-tetramethylindan-2-thione (**1c**).[18] The reaction of **1c** with lithiated methoxyallene **9** was performed as in the case of **1a** and **1b**, but it led to a different result (Scheme 8). The ^1H NMR spectrum of the crude mixture did not reveal the presence of the expected vinylthiirane similar to compounds **18** or **21**. Instead, two pseudo-triplets clearly were found at 2.37 and 2.76 ($J=7.4$ Hz each) ppm, thus suggesting the presence of an ethylene bridge. Most significantly, a signal for the methoxy group was missing, and the IR and ^{13}C NMR spectra showed the presence of a carbonyl group. The 2D-NMR measurements confirmed the location of the carbonyl group



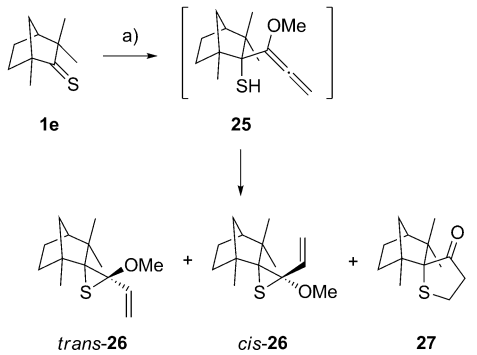
Scheme 8. Reaction of lithiated methoxyallene **9** with tetramethylindanthione **1c** providing spiro compound **24**: a) lithiated methoxyallene **9** (3.0 equiv), THF, −78 °C to −40 °C, 1 h, then H_2O, rt, 1 h.

at the C-3 position of a dihydrothiophene ring. The structure of the isolated product unambiguously indicates that in this case the attack of the methoxyallenyl anion again occurs in a carbophilic fashion to give thiol **22**, but instead of the 1,3-cyclization a 1,5-cyclization proceeds, thus leading to 2,5-dihydrothiophene intermediate **23**. Apparently, the initially formed enol ether moiety of **23** easily undergoes hydrolysis during the aqueous work-up, yielding the isolated ketone **24**. The different cyclization behavior of thiol **22** compared to **17** and **20** is quite surprising and probably caused by the steric pressure exerted by the four methyl groups.

Reactions of lithiated methoxyallene **9** with enolizable thiocamphor **1d** (Figure 1) were also tested, but in this case the starting material was fully recovered. It is likely that **1d** is only deprotonated by **9** forming the corresponding enethiolate, which upon quenching with water is reconverted into the starting thioketone. The experiment with non-enolizable thiofenchone **1e** did also not give the expected adduct with **9** under standard conditions. The high steric hindrance prevents addition at low temperature, and treatment of **1e** with 12 equivalents of lithiated methoxyallene **9** and warming up to −20 °C for 3 h resulted at least in a partial conversion (<30 %) of the starting material. In the ^{1}H NMR spectrum of the crude product mixture two sets of signals attributed to vinyl substituents (in ca. 3:1 ratio) were found. In addition, two characteristic pseudo-triplets indicating the formation of a dihydrothiophene derivative were observed along with signals of unidentified products. Unfortunately, none of the products could be isolated in pure state. The formation of *cis*- and *trans*-thiirane **26** and the dihydrothiophene derivative **27** (ratio ca. 2:1) suggest that the carbophilic addition of lithiated methoxyallene **9** onto **1e** selectively occurs to the *exo*-face of the norbornane skeleton.[19] The resulting allenyl thiol **25** subsequently undergoes competitive 1,3- or 1,5-cyclization to produce **26** and **27** (total yield ca. 25 %; Scheme 9).

Finally, the sterically extremely crowded di-*tert*-butylthioketone (**1f**) was also included in the study and its reaction with **9** resulted in the formation of a complex mixture of unidentified products. Formation of neither thiirane nor dihydrothiophene derivatives could be detected based on the ^{1}H NMR spectrum of the crude product mixture. Attempted purification did not result in the isolation of pure compounds.

The presented examples demonstrate that lithiated methoxyallene **9** reacts with thioketones to yield, after protonation, allenyl thiols that cannot be isolated due to their spontaneous cyclization. It is likely that the higher acidity of thiols allows an autocatalytic process by protonation at the central carbon of the electron-rich allenyl moiety and subsequent cyclization of the resulting allyl cation either as 1,3-cyclization



Scheme 9. Reaction of thiofenchone **1e** with an excess of lithiated methoxyallene **9**: a) **9** (12.0 equiv), THF, −40 °C to −20 °C, 3 h.

to vinylthiiranes or as 1,5-cyclization to dihydrothiophene derivatives. The latter process is apparently favored when sterically very demanding substrates such as **1c** and **1e** are the precursors. It is not clear at the moment whether conformational effects caused by the methyl groups in these intermediates are responsible for this selectivity switch or whether other factors are operating. As key conclusion can be stated that the allenyl thiols derived from alkoxyallenes and thioketones do not require an external Brønsted or Lewis acidic catalyst for the cyclizations.[20]

By contrast, the allenyl alcohols obtained from the corresponding ketones can be isolated and they lead either to vinyloxiranes or to 2,5-dihydrofurans depending on the substrate and on the type of the catalyst applied. Whereas in certain cases traces of acid lead to slow 1,3-cyclization, addition of catalytic amounts of Au^I/pyridine-complex or of base leads preferentially to the five-membered product. In this series, the formation of the strained three-membered ring compounds is only observed with sterically hindered systems. A straightforward rationale for these results is still not possible.

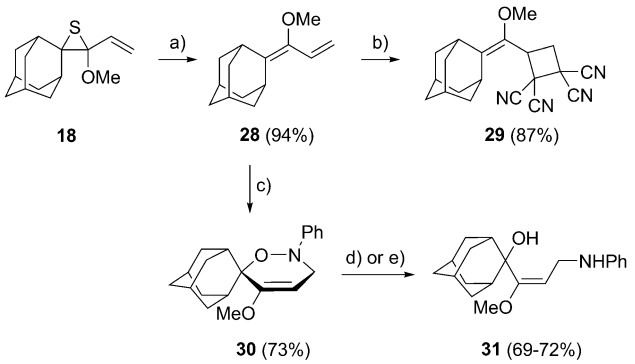
Calculations of the reaction pathways including the transition states of the catalyzed processes may help to understand the reaction mechanism and the differences. To begin this theoretical treatment, the relative energies of the precursors, the intermediates, and the products were calculated by DFT methods (B3LYP/6-311+G(d,p) level, gas phase). We selected acetone and thioacetone as simple but characteristic model electrophiles. The energies, as compiled in Table 2, show substantial differences in the two series. The most striking, but not surprising difference is the large

Table 2. Relative energies of model compounds and intermediates according to DFT calculation (B3LYP/6-311+G(d,p) level) in the gas phase.

Compounds	kJ mol^{-1}	Compounds	kJ mol^{-1}
Methoxyallene	0	Methoxyallene	0
+Acetone		+Thioacetone	
Primary Adduct	−14.2	Primary Adduct	−58.4
Vinyloxirane	−40.8	Vinylthiirane	−120.0
Dihydrofuran	−112.0	Dihydrothiophene	−186.5

energy gain by the addition of methoxyallene to thioacetone (−58.4 kJ mol^{-1}) compared to that to acetone (−14.2 kJ mol^{-1}). The higher energy gain in this step can be attributed to the higher energy level of the thiocarbonyl group. For the next step, the rearrangement to a vinylthiirane or a vinyloxirane, again a dramatically higher energy gain was calculated for the sulfur system (−61.8 versus −26.6 kJ mol^{-1}). We can speculate that the more exothermic reaction step also involves a lower energy barrier; however, we should bear in mind that these steps are catalyzed processes. Comparing finally the strained vinylthiiranes/oxiranes with the unstrained five-membered heterocycles reveals the last energy gain of the system, which is in the range of −65 kJ mol^{-1} for both series.

Having the new thiirane **18** in hand, its desulfurization with tris(diethylamino)phosphine[21] was carried out in order to prepare the hitherto unknown electron-rich 2-methoxydiene **28**. This reaction occurred smoothly in refluxing tetrahydrofuran yielding the desired diene **28** in an excellent yield of 94% (Scheme 10). The alternative thermal sulfur extrusion by boiling of **18** in toluene also led to **28**, but the yield was considerably lower (35%). Because many adamantane-derived compounds are known as biologically active compounds,[22] the new 1,3-diene **28** bearing an adamantanylidene moiety could be an attractive building block for the synthesis of complex molecules. For example, [4+2] cycloadditions with active (hetero)dienophiles should offer a straightforward method for the preparation of diverse six-membered products. We therefore examined the reactions of diene **28** with selected electron-deficient dienophiles.



Scheme 10. Synthesis and transformations of methoxy-substituted 1,3-diene **28**: a) $P(NEt_2)_3$ (1.2 equiv), THF, reflux, 1 h; b) tetracyanoethylene (1.0 mmol), CH_2Cl_2, rt, 2 d; c) PhNO (1.3 equiv), CH_2Cl_2, rt, 3 d; d) SmI_2, THF, 2 h; e) H_2 (balloon pressure), Pd/C, MeOH/AcOEt, rt, 24 h.

In the first experiment tetracyanoethylene (TCNE) was combined with **28**. After two days at room temperature, both in dichloromethane or in tetrahydrofuran, the conversion was complete, and a single product was identified in the crude reaction mixture. After filtration through a silica gel pad, this compound was isolated as analytically pure solid (87% yield, Scheme 10). The ^{1}H NMR spectrum revealed the presence of a methoxy signal along with a group of three signals (dd and 1H each) at 4.43 (J=8.7, 11.1 Hz), 3.46 (J=11.1, 12.2 Hz), and 3.09 (J=8.7, 12.2 Hz) ppm. In the ^{13}C NMR spectrum, two singlets attributed to C=C (both *i*-C-atoms) were found at 142.7 and 136.0 ppm. These data fit to alkenyl-substituted cyclobutane derivative **29**. It is well known that other 1,1-disubstituted buta-1,3-dienes and TCNE produce cyclobutanes in step-wise thermal [2+2] cycloadditions.[23] No rearrangement of **29** into the corresponding cyclohexene derivative was observed. Unexpectedly, the electron-deficient dimethyl dicyanofumarate, known as a reactive Michael acceptor[24a] and dienophile,[24b] did not undergo the reaction with **28** even after seven days at room temperature. Extremely reactive fluorinated alkenes such as *trans*-1,2-bis(trifluoromethyl)-1,2-dicyanoethylene[24c] and 1,1-bis(trifluoromethyl)-2,2-dicyanoethylene[24d] were also unreactive towards 1,3-diene **28**. Very likely, steric hindrance caused by the bulky adamantane moiety is the reason for the observed inertness of **28**.

Gratifyingly, the reaction of diene **28** with nitrosobenzene occurred smoothly at room temperature, and after three days a colorless solid was obtained as the major product. The spectroscopic analysis confirmed the structure of the expected [4+2] cycloadduct. For example, the diagnostic signals of the enol ether moiety were found in the NMR spectra: a pseudo-triplet ($J\approx$2.7 Hz) at 4.37 ppm attributed to 4-H in the ^{1}H NMR spectrum and signals of C-4 and C-5 at 89.9 and 160.5 ppm, respectively, in the ^{13}C NMR spectrum. The synthetic utility of diverse 1,2-oxazine derivatives leading to polyfunctionalized compounds of potentially biological significance is well documented.[25] For that reason, cycloadduct **30** was treated with an excess of SmI_2 to give unsaturated amino alcohol **31** in 72% yield.[26] A surprising resistance of the 3,6-dihydro-1,2-oxazine **30** to undergo exhaustive hydrogenation was observed employing palladium on charcoal as a catalyst. Amino alcohol **31** was obtained as a sole product in comparable yield of 69% after 24 h. The structure of the latter was unambiguously confirmed based on spectroscopic data, for example, signals of the C=C bond at 99.6 and 161.2 ppm in the ^{13}C NMR spectrum.

Conclusions

The present study shows that lithiated methoxyallene easily reacts with non-enolizable cycloaliphatic thioketones and that in all cases carbophilic attack of the nucleophile occurs. In the case of the enolizable thiocamphor **1d** no addition was observed, probably due to deprotonation of the thioketone. The primary thiols formed by addition of the allenyl

moiety underwent spontaneous cyclization yielding either vinylthiirane or 2,5-dihydrothiophene derivatives that easily hydrolyze to ketones. The mode of the cyclization process depends on the structure of the starting thioketones. Whereas the non-enolizable representatives bearing the CH atoms at the α position tend to form vinylthiiranes as a result of 1,3-heterocyclization, the alternative 1,5-ring closure is observed for sterically more demanding thioketones substituted with Me groups at the α-position. Although not many examples of vinylthiiranes are known in the literature,[27] they are attractive starting materials for further conversions. The method presented in our study offers a unique protocol for their synthesis. Subsequent desulfurization of one of the vinylthiiranes led to an electron-rich methoxy-substituted 1,3-diene that underwent cycloaddition only with sterically less demanding electron-deficient dienophiles such as TCNE and nitrosobenzene. With TCNE, a [2+2] cycloaddition to a vinylcyclobutane derivative was observed, whereas the nitroso compound underwent a hetero Diels–Alder reaction. The resulting 1,2-oxazine derivative can be used for the preparation of γ-amino alcohols potentially useful for further applications.

Experimental Section

Experimental details and all analytical data including copies of the NMR spectra are given in the Supporting Information.

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[1] a) F. A. Carey, R. J. Sundberg in *Advanced Organic Chemistry Part B: Reactions and Synthesis, 5th ed.*, Springer, New York, **2007**, pp. 637–649; b) H. Yamataka, K. Yamada, K. Tomioka in *Addition of Organolithium Reagents to Double Bonds. Patai's Chemistry of Functional Groups*, Wiley, **2009**; c) M. Schlosser in *Organometallics in Synthesis Third Manual*, Wiley, New Jersey, **2009**, pp. 107–112.

[2] Reviews: a) W. M. McGregor, D. C. Sherrington, *Chem. Soc. Rev.* **1993**, *22*, 199–204; b) K. Okuma, *Sulfur Rep.* **2002**, *23*, 209–241; see also: c) E. Vedejs, D. A. Perry, R. G. Wilde, *J. Am. Chem. Soc.* **1986**, *108*, 2985–2989; d) R. Okazaki, A. Ishii, N. Inamoto, *J. Am. Chem. Soc.* **1987**, *109*, 279–280.

[3] a) R. Mayer, J. Morgenstern, J. Fabian, *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 277–286; *Angew. Chem.* **1964**, *76*, 157–167; b) J. Voss in *Methoden der Organischen Chemie, Band E11* (Houben-Weyl) (Ed.: D. Klamann), Georg Thieme Verlag, Stuttgart, **1985**, pp. 188–231.

[4] a) R. Huisgen, E. Langhals, *Heteroat. Chem.* **2006**, *17*, 433–442; b) D. S. C. Black, K. G. Watson, *Aust. J. Chem.* **1973**, *26*, 2491–2504; c) R. Huisgen, L. Fišera, H. Giera, R. Sustmann, *J. Am. Chem. Soc.* **1995**, *117*, 9671–9678; d) R. Huisgen, J. Rapp, *Tetrahedron* **1997**, *53*, 939–960; e) R. Huisgen, X. Li, H. Giera, E. Langhals, *Helv. Chim. Acta* **2001**, *84*, 981–999.

[5] a) L. Fišera, R. Huisgen, I. Kalwinsch, E. Langhals, X. Li, G. Mlostoń, K. Polborn, J. Rapp, W. Sicking, R. Sustmann, *Pure Appl. Chem.* **1996**, *68*, 789–798; b) G. Mlostoń, H. Heimgartner in *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products* (Eds.: A. Padwa, W. H. Pearson), Wiley, New York, **2002**, pp. 315–360; c) G. Mlostoń, H. Heimgartner, in *Targets in Heterocyclic Systems, Vol. 10* (Eds.: O. A. Attanasi, D. Spinelli), Italian Society of Chemistry, **2006**, pp. 266–300.

[6] M. T. Molina, M. Yánez, O. Mó, R. Notario, J.-L. M. Abboud in *The Chemistry of Double-Bonded Functional Groups, Supplement A3* (Ed.: S. Patai), Wiley, **1997**, Chap. IV, pp. 1439–1442.

[7] a) D. Paquer, M. Vazeux, *J. Organomet. Chem.* **1977**, *140*, 257–264; b) A. Alberti, M. Benaglia, D. Macciantelli, M. Marcaccio, A. Olmeda, G. F. Pedulli, S. Roffia, *J. Org. Chem.* **1997**, *62*, 6309–6315.

[8] a) P. Metzner, J. Vialle, A. Vibet, *Tetrahedron Lett.* **1976**, *17*, 4295–4296; b) P. Metzner, J. Vialle, A. Vibet, *Tetrahedron* **1978**, *34*, 2289–2294.

[9] a) K. B. Wiberg, A. L. Bartelson, W. F. Bailey, *Tetrahedron Lett.* **2011**, *52*, 2169–2171; b) W. F. Bailey, A. L. Bartelson, K. B. Wiberg, *J. Am. Chem. Soc.* **2012**, *134*, 3199–3207.

[10] A. Ohno, K. Nakamura, M. Uohama, S. Oka, *Chem. Lett.* **1975**, 983–984.

[11] G. Mlostoń, E. Obijalska, K. Urbaniak, H. Heimgartner, *Heteroat. Chem.* **2008**, *19*, 182–187.

[12] C.-E. Lin, S. K. Richardson, W. Wang, T. Wang, D. S. Garvey, *Tetrahedron* **2006**, *62*, 8410–8418.

[13] Reviews: a) M. Brasholz, H.-U. Reissig, R. Zimmer, *Acc. Chem. Res.* **2009**, *42*, 45–56; b) R. Zimmer, H.-U. Reissig, *Chem. Soc. Rev.* **2014**, *43*, 2888–2903.

[14] a) S. Hoff, L. Brandsma, J. F. Arens, *Recl. Trav. Chim. Pays-Bas* **1969**, *88*, 609–619; b) P. Magnus, P. Albaugh-Robertson, *J. Chem. Soc. Chem. Commun.* **1984**, 804–806; c) S. Hormuth, H.-U. Reissig, *J. Org. Chem.* **1994**, *59*, 67–73; d) M. Brasholz, H.-U. Reissig, *Angew. Chem. Int. Ed.* **2007**, *46*, 1634–1637; *Angew. Chem.* **2007**, *119*, 1659–1662; e) M. Brasholz, H.-U. Reissig, *Synlett* **2007**, 1294–1298; f) M. Brasholz, B. Dugovič, H.-U. Reissig, *Synthesis* **2010**, 3855–3864.

[15] a) R. Huisgen, G. Mlostoń, K. Polborn, F. Palacios-Gambra, *Liebigs Ann./Recl.* **1997**, 187–192; b) M. Dawid, G. Mlostoń, J. Warkentin, *Org. Lett.* **2001**, *3*, 2455–2456; c) S. Leśniak, G. Mlostoń, K. Urbaniak, P. Wasiak, A. Linden, H. Heimgartner, *Tetrahedron* **2006**, *62*, 7776–7782; d) V. A. Nikolaev, A. V. Ivanov, L. L. Rodina, G. Mlostoń, *Beilstein J. Org. Chem.* **2013**, *9*, 2751–2761.

[16] An attempted purification of compound **12** on silica gel (dichloromethane) resulted in complete decomposition and provided enone **14** almost exclusively. For acidic hydrolysis of allenyl alcohols see: S. Hoff, L. Brandsma, J. F. Arens, *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 1179–1184, and ref. [14c].

[17] a) N. A. Ross, R. A. Bartsch, A. P. Marchand, *Arkivoc* **2003**, *(xii)*, 27–30; b) J. Romański, G. Mlostoń, H. Heimgartner, *Helv. Chim. Acta* **2007**, *90*, 1279–1288; c) R. Zimmer, M. Taszarek, L. Schefzig, H.-U. Reissig, *Synlett* **2008**, 2046–2050.

[18] a) R. Okazaki, A. Ishii, N. Inamoto, *Tetrahedron Lett.* **1984**, *25*, 5147–5150; b) R. Huisgen, E. Langhals, H. Noeth, *J. Org. Chem.* **1990**, *55*, 1412–1414.

[19] a) B. Koning, R. Hulst, A. Bouter, J. Buter, A. Meetsma, R. M. Kellogg, *Chem. Commun.* **1997**, 1065–1066; b) R. Huisgen, G. Mlostoń, A. Pröbstl, *Heteroat. Chem.* **2001**, *12*, 136–145; see also ref. [12].

[20] For the gold-catalyzed cyclization of allenyl thiols without alkoxy groups, see: a) N. Morita, N. Krause, *Angew. Chem. Int. Ed.* **2006**, *45*, 1897–1899; *Angew. Chem.* **2006**, *118*, 1930–1933; b) K. Ando, *J. Org. Chem.* **2010**, *75*, 8516–8521.

[21] a) G. Mlostoń, K. Urbaniak, S. Leśniak, P. Wasiak, H. Heimgartner, *Heterocycles* **2007**, *72*, 541–552; b) G. Mlostoń, K. Urbaniak, A. Linden, H. Heimgartner, *Tetrahedron* **2009**, *65*, 8191–8198.

[22] a) G. Lamoureux, G. Artavia, *Curr. Med. Chem.* **2010**, *17*, 2967–2978; b) L. Wanka, K. Iqbal, P. R. Schreiner, *Chem. Rev.* **2013**, *113*, 3516–3604.

[23] a) C. A. Stewart, Jr., *J. Am. Chem. Soc.* **1962**, *84*, 117–118; b) J. J. Eisch, G. R. Husk, *J. Org. Chem.* **1966**, *31*, 589–591; c) N. Shimizu, S. Nishida, *J. Chem. Soc. Chem. Commun.* **1978**, 931–932; d) C. Rücker, D. Lang, J. Sauer, H. Friege, R. Sustmann, *Chem. Ber.* **1980**, *113*, 1663–1690; e) F. Kataoka, N. Shimizu, S. Nishida, *J. Am. Chem. Soc.* **1980**, *102*, 711–716; f) H. Pizem, O. Sharon, A. A. Frimer, *Tetrahedron* **2002**, *58*, 3199–3205.

[24] a) G. Mlostoń, H. Heimgartner, *Helv. Chim. Acta* **2006**, *89*, 442–449; b) R. Sustmann, S. Trappauchai, H. Bandmann, *J. Am. Chem. Soc.* **1996**, *118*, 12555–12561; c) R. Huisgen, G. U. Desmaison, *Helv. Chim. Acta* **2012**, *95*, 1049–1063; d) R. Huisgen, R. Brückner, *J. Org. Chem.* **1991**, *56*, 1679–1681.

[25] For selected examples, see a) B. Bressel, B. Egart, A. Al-Harrasi, R. Pulz, H.-U. Reissig, I. Brüdgam, *Eur. J. Org. Chem.* **2008**, 467–474; b) B. Bressel, H.-U. Reissig, *Org. Lett.* **2009**, *11*, 527–530; c) M. Jasiński, D. Lentz, E. Moreno-Clavijo, H.-U. Reissig, *Eur. J. Org. Chem.* **2012**, 3304–3316; d) M. Jasiński, D. Lentz, H.-U. Reissig, *Beilstein J. Org. Chem.* **2012**, *6*, 662–674; e) C. Parmeggiani, F. Cardona, L. Giusti, H.-U. Reissig, A. Goti, *Chem. Eur. J.* **2013**, *19*, 10595–10604; f) M. Jasiński, E. Moreno-Clavijo, H.-U. Reissig, *Eur. J. Org. Chem.* **2014**, 442–454; g) L. Bouché, M. Kandziora, H.-U. Reissig, *Beilstein J. Org. Chem.* **2014**, *10*, 213–223; see also reviews: h) F. Pfrengle, H.-U. Reissig, *Chem. Soc. Rev.* **2010**, *39*, 549–557; i) L. Bouché, H.-U. Reissig, *Pure Appl. Chem.* **2012**, *84*, 23–36.

[26] a) J. L. Chiara, C. Destabel, P. Gallero, J. Marco-Contelles, *J. Org. Chem.* **1996**, *61*, 359–360; b) G. E. Keck, T. T. Wager, S. F. McHardy, *Tetrahedron* **1999**, *55*, 11755–11772; c) J. Revuelta, S. Cicchi, A. Brandi, *Tetrahedron Lett.* **2004**, *45*, 8375–8377; for SmI_2-promoted reduction of 3,6-dihydro-2*H*-1,2-oxazines, see: d) M. Jasiński, T. Watanabe, H.-U. Reissig, *Eur. J. Org. Chem.* **2013**, 605–610.

[27] a) M. P. Schneider, M. Schnaithmann, *J. Am. Chem. Soc.* **1979**, *101*, 254–256; b) M. Goldbach, E. Jäkel, M. P. Schneider, *J. Chem. Soc. Chem. Commun.* **1987**, 1434–1435; c) H. Bader, H. Hopf, K. Sieper, *Chem. Ber.* **1989**, *122*, 383–384; d) I. Maciągiewicz, P. Dybowski, A. Skowrońska, *Tetrahedron Lett.* **1999**, *40*, 3791–3794; e) R. D. Adams, J. L. Perrin, *J. Am. Chem. Soc.* **1999**, *121*, 3984–3991; f) M. Hamaguchi, N. Funakoshi, T. Oshima, *Tetrahedron Lett.* **1999**, *40*, 8117–8120; g) C. Larksarp, O. Sellier, H. Alper, *J. Org. Chem.* **2001**, *66*, 3502–3506; h) E. Rogers, H. Araki, L. A. Batory, C. E. McInnis, J. T. Njardarson, *J. Am. Chem. Soc.* **2007**, *129*, 2768–2769; i) A. Bellomo, D. Gonzalez, *Tetrahedron Lett.* **2007**, *48*, 3047–3051; j) E. A. Ilardi, J. T. Njardarson, *J. Org. Chem.* **2013**, *78*, 9533–9540.

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