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Synthesis of Sulphur-Containing Heterocycles by Ring Closing Diene Metathesis

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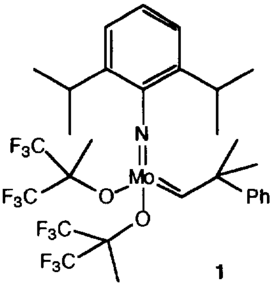
Abstract: We have shown that, surprisingly, the Schrock molybdenum alkylidene catalyst **1** can perform ring closing metathesis reactions on substrates containing a sulphide group, converting diallyl sulphide **5** to 2,5-dihydrothiophene **6** with >99 % conversion. By contrast, the ruthenium alkylidene catalyst **2**, which is generally more tolerant of functional groups in the substrate, is unreactive towards diallylsulphide. However even the molybdenum catalyst **1** proved unable to catalyse ring closure of tetrathiafulvalene derivative **7**. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

Since the appearance in 1992 and 1993 of the seminal papers by Grubbs on the use of molybdenum-[1] and ruthenium-[2] based alkylidene catalysts **1** and **2** for the synthesis of cyclic alkenes, many organic chemists have begun to exploit this powerful method of ring closure. However, the scope and limitations of these catalysts are still very imperfectly known, particularly with respect to substrates containing second-row heteroatoms. This communication describes some of our findings regarding the tolerance of catalysts **1** and **2** for substrates bearing sulphur-containing functional groups.



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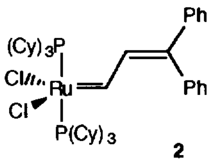

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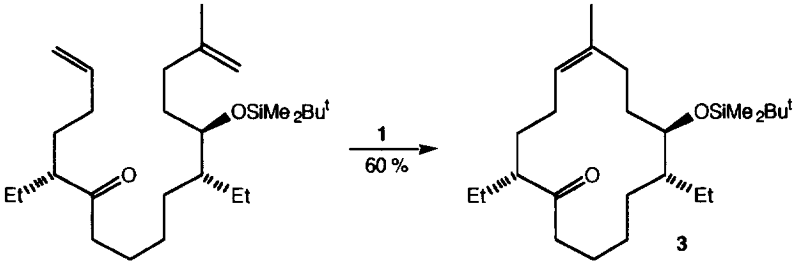
The original papers[1] of Grubbs and Fu concerned the molybdenum alkylidene **1**, and showed that it could be used to make 5-, 6- and 7-membered carbo- and hetero-cycles. They also showed that it would tolerate a very limited range of functional groups, including esters, tertiary amides, tertiary amines, acetals, ethers and silyl ethers.[1] However, these original communications seem almost to have defined the scope of catalyst **1** in organic synthesis. Since then, its use has been extended to include ketonic substrates,[3] and in natural product syntheses the formation of 8- and 14-membered lactams,[4] including **3**, during the synthesis of the fluviricin B_1 aglycone. However, this catalyst is extremely sensitive to the presence of oxygen, water, and acidic functionalities including alcohols and carboxylic acids. These restrictions, coupled with the difficulty of storing it for any length of time (a refrigerated glove box is recommended), have limited the synthetic applications of catalyst **1**.



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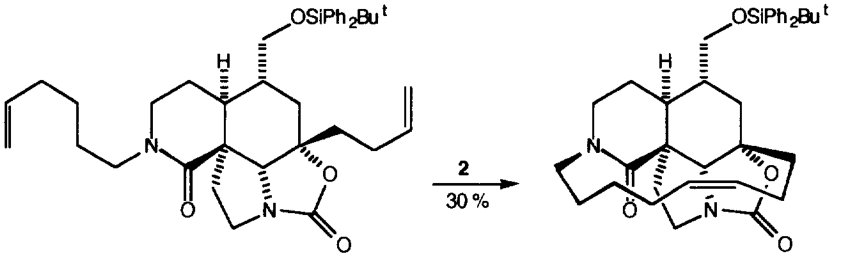
By contrast, ruthenium alkylidene **2** tolerates substrates containing alcohols, aldehydes and carboxylic acids, as well as acetals, silyl ethers, amides etc..[2] Its tolerance for amines is low, but this can be overcome by protonation or protection. Because of its greater tolerance for various functional groups, this catalyst can be used in a much wider range of solvents, including alcohols, and rigorous drying and degassing is no longer essential.[2] This catalyst has now been very widely used, by Grubbs[5] and many others,[6] for synthesis of 5- to 13-membered carbo- and hetero-cycles. Applications have included syntheses of cyclic peptides and peptide analogues, as well as approaches to natural products, including the bridging macrocyclic lactam **4**, *en route* to manzamine A.[7]



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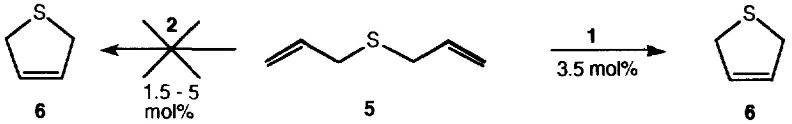
However, despite the increasingly wide-spread use of ring closing metathesis as a synthetic technique, the tolerance of catalysts **1** and **2** for functional groups involving second-row elements has yet to be thoroughly investigated. As part of a programme to investigate the scope of ring closing metathesis for organic synthesis, we now report the tolerance of metathesis catalysts for sulphur-containing substrates.

RESULTS AND DISCUSSION

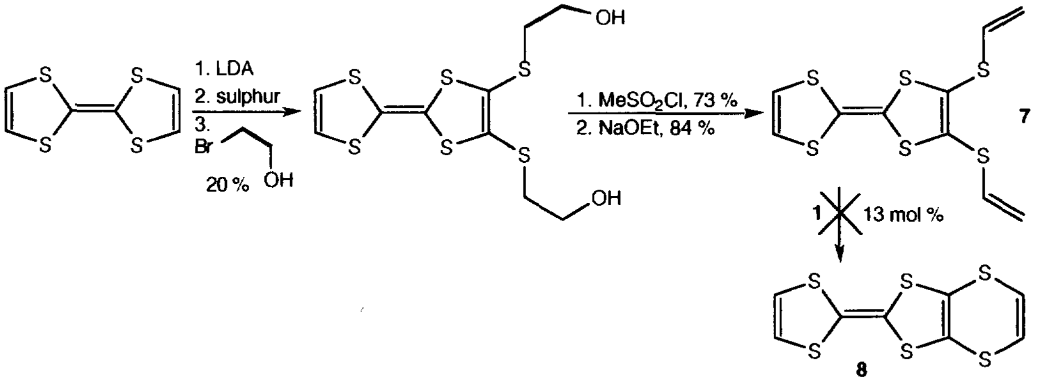
As a test compound, we chose readily available diallyl sulphide **5**, which we hoped to cyclise to 2,5-dihydrothiophene **6**. 2,5-Dihydrothiophene is surprisingly difficult of access: outside the patent literature,[8] published syntheses are either low-yielding,[9] or involve very hazardous materials. Thus **6** may be obtained from thiophene using a mixture of zinc, trifluoroacetic acid and lithium perchlorate;[10] or by treatment of butenyne with NaSH.[11] A new, convenient, high-yielding route to 2,5-dihydrothiophene is therefore of considerable interest.

Diallyl sulphide **5** was carefully purified by washing with 5 % NaOH then water, drying with $MgSO_4$, and distilling from calcium hydride, and was degassed by repeated freeze-pump-thaw cycles. Treatment with molybdenum alkylidene **1** in dry, degassed toluene overnight was followed by short-path reduced pressure distillation, giving a solution of 2,5-dihydrothiophene **6** in toluene, with less than 1 % of uncyclised material apparent in the ^{1}H NMR spectrum. Integrals of the ^{1}H NMR signals for toluene and heterocycle **6** show that the yield is essentially quantitative, but because of the large ratio of toluene to **6** an accurate yield could not be calculated.[12] We now believe overnight reaction to be unnecessary: with catalyst **1**, reaction apprently proceeds very rapidly or not at all. The catalyst is extremely sensitive to both oxygen and water, and decomposition from an orange to an inactive darker brown solution is rapid under reaction conditions. NMR experiments (see below) show that unchanged catalyst **1** may persist for an hour in a well sealed vessel, but colour changes suggest that this is unusual. Decomposition may be slower in the absence of acceptable substrate, perhaps because the metallacyclobutane intermediate in the catalytic cycle is more liable to decomposition than the metal alkylidene.

Because of the difficulty of separating 2,5-dihydrothiophene **6** from toluene, diallyl sulphide **5** was treated with the ruthenium catalyst **2** in the absence of solvent. Using diallyl ether, we have shown that metathesis generally proceeds well in the absence of solvent, provided polymerisation does not compete.[13] In particular, we have cyclised diallyl ether both in toluene (96 % conversion, 1.6 mol% of **1**) and in the absence of solvent (59 % conversion, 0.22 mol% of **1**); again, problems were found in separating 2,5-dihydrofuran from solvent. However, after repeated treatments of purified, degassed diallylsulphide with ruthenium alkylidene **2**, we have never obtained 2,5-dihydrothiophene. Up to 87 % of the diallyl sulphide is recovered unchanged. In general, catalyst **2** is much more tolerant of air and moisture than is **1**, and the original orange colour of the solution may persist for two days in a septum-capped flask. By contrast, in the presence of **6**, the green-black colour associated with decomposition products develops in a few hours.



Following the successful formation of 2,5-dihydrothiophene using molybdenum alkylidene **1**, we attempted to extend this methodology to the synthesis of a tetrathiafulvalene derivative, **8**. Tetrathiafulvalene **8** forms salts with interesting electrical properties,[14] but its synthesis by a mixed coupling reaction is unsatisfactory, since the self-coupled products form more readily, and **8** is obtained in only 1.4 % yield after two steps.[15] Unsymmetrical functionalisation of tetrathiafulvalene itself is a much more attractive approach. We therefore sought to prepare tricyclic tetrathiafulvalene **8** by ring closing metathesis on the *bis*-vinylsulphide **7**, prepared in three steps from tetrathiafulvalene as shown below.[16] Diene **7** is insoluble in toluene; catalyst **1** has been shown to tolerate chlorinated solvents, so a solution of diene **7** in dry CH_2Cl_2 was degassed by freeze-pump-thaw cycles and transferred by cannula onto the catalyst **1**. Following the reaction by ^1H NMR showed, disappointingly, no change in either starting material or catalyst, until the latter gradually deteriorated after about an hour; the original orange colour of the solution persisted for longer than usual on this occasion. The ring-closed product **8** was never detected.



CONCLUSIONS

We have shown that ring closing metathesis can be performed on sulphur-containing substrates. Molybdenum alkylidene **1** is the catalyst of choice for this reaction, and even this catalyst may be inactive towards polysulphur organic substrates. Research is in progress to investigate the compatability of catalysts **1** and **2** with phosphorus-containing substrates.

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