Pergamon

Tetrahedron Letters 41 (2000) 1615–1618

TETRAHEDRON LETTERS

Lewis acid mediated cascade reactions of silyl-substituted methylenecyclopropyl ketones

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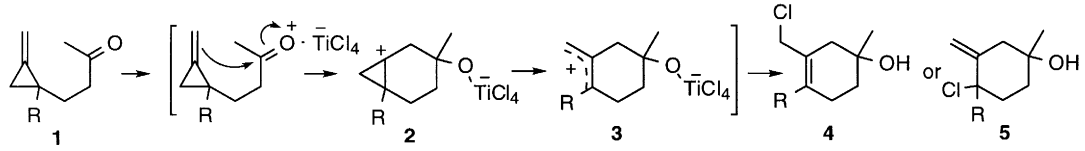
Received 3 November 1999; accepted 16 December 1999

Abstract

The Lewis acid mediated cyclisation of various silyl-substituted methylenecyclopropyl ketones has been investigated. The presence of the silyl-substituent enhances the reactivity of the methylene cyclopropane in comparison to our earlier study on non-silyl-substituted methylenecyclopropyl ketones, allowing milder Lewis acids ($BF_3 \cdot Et_2O$ or $BF_3 \cdot 2AcOH$) to be used for the cyclisation reaction. The mild conditions used allow the allyl cation, formed as an intermediate in the cyclisation, to be trapped in further carbon–carbon bond-forming reactions.

Keywords: methylenecyclopropane; Lewis acid; cascade; cyclisation.

We recently reported that treatment of methylenecyclopropyl ketones or aldehydes such as **1** (R=H) with suitable Lewis acids ($TiCl_4$ or $SnCl_4$) provides a new route to cycloalkanols.[1] The mechanism for this reaction is presumed to proceed by nucleophilic addition of the alkene to the activated carbonyl, leading to a cyclopropyl cation intermediate **2**, which rearranges to an allyl cation **3**, which, in turn, is trapped by chloride anion derived from the Lewis acid (Scheme 1).[2]



Scheme 1.

Incorporation of a silyl-substituent on the methylenecyclopropane precursor (e.g. **1**, R=SiR_3) should serve to encourage the initial alkene addition to the carbonyl, since the silyl group should stabilise the intermediate cyclopropyl cation[3] — indeed the silyl-substituted methylenecyclopropane **1** is, of course,

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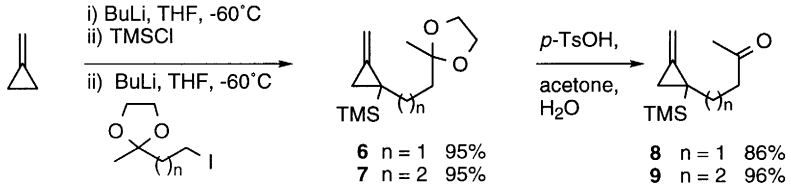
0040-4039/00/$ - see front matter
PII: S0040-4039(99)02342-4

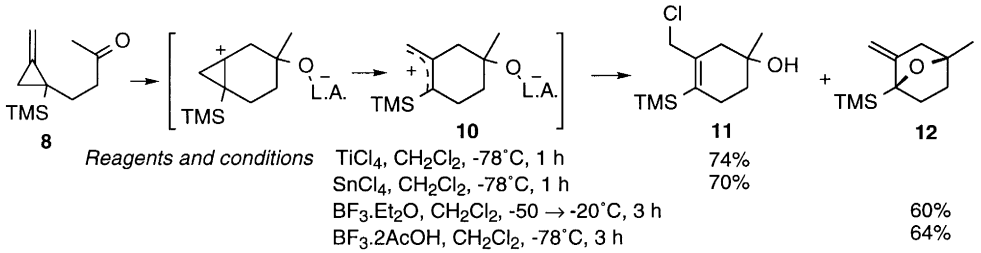
a strained allylsilane.[4] In this paper, we describe our studies with such silyl-substituted methylenecyclopropyl ketones, which have led to the development of a novel, Lewis acid mediated, cascade process.

Preparation of suitable silylated methylenecyclopropyl ketones was readily accomplished by sequential deprotonation of methylenecyclopropane, silylation, deprotonation and alkylation with an iodoketal, carried out in a one-pot procedure, [5] followed by ketal deprotection (Scheme 2).



Scheme 2.

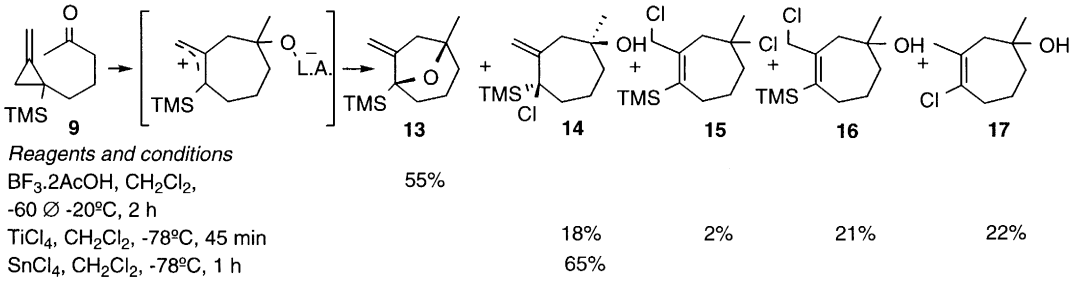
Cyclisation of ketone **8** using $TiCl_4$ or $SnCl_4$ gave cyclohexene **11**,[6] formed by trapping the intermediate allyl cation **10** with chloride ion, in good yield (Scheme 3).



Scheme 3.

In contrast, the analogous non-silylated methylenecyclopropyl ketone (**1**, R=H) required higher reaction temperatures and gave lower yields of cyclised products when treated with $TiCl_4$ or $SnCl_4$.[1] Furthermore, whereas the non-silylated methylenecyclopropyl ketones had failed to react with milder Lewis acids such as boron trifluoride,[1] when treated with either $BF_3 \cdot Et_2O$ or $BF_3 \cdot 2AcOH$ ketone **8** gave the unusual bicyclic ether **12** in good yield. Here, in the absence of a sufficiently nucleophilic anion derived from the Lewis acid, the intermediate allyl cation **10** is trapped intramolecularly by the alkoxide nucleophile.[7]

Cyclisation of the homologous silylated ketone **9** with $BF_3 \cdot 2AcOH$ similarly gave the bicyclic ether **13** in reasonable isolated yield (Scheme 4).

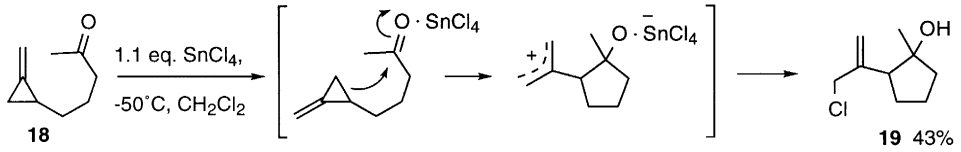


Scheme 4.

Treatment of **9** with $TiCl_4$, however, led to a complex mixture from which four compounds **14**–**17**, all presumably derived from an allyl cation intermediate, were isolated, with vinyl chloride **17** presumably

resulting from a protodesilylation of an allylsilane intermediate cf. **14**. Using $SnCl_4$, on the other hand, cleanly gave *cis* hydroxychloride **14** as the only isolated product in 65% yield.[8]

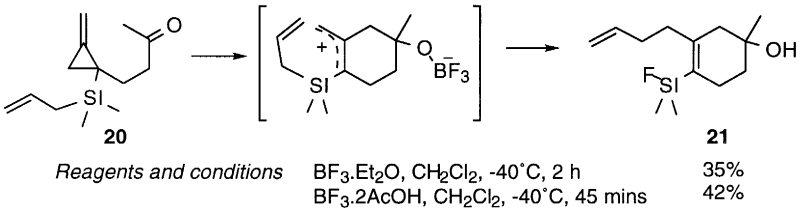
The cyclisation of ketone **9** to give seven-membered ring products is in stark contrast to the cyclisation of the non-silylated analogue **18**, which on treatment with $TiCl_4$ or $SnCl_4$ gave cyclopentanol **19**, via nucleophilic attack by the σ-bond of the methylenecyclopropane (Scheme 5).[1]



Scheme 5.

In our earlier work we sought to trap the allyl cation, formed as an intermediate in these cyclisations, with a range of nucleophilic groups grafted on to the starting methylenecyclopropyl ketone. However, most of these attempts were thwarted by rapid trapping of the allyl cation by chloride ion derived from the Lewis acid $TiCl_4$ or $SnCl_4$, which were required for the cyclisation. The introduction of a silyl-substituent, however, allows the cyclisation to be carried out in the absence of a strongly nucleophilic counteranion, so we again sought to exploit the reactivity of the intermediate allyl cation for further reaction. To this end we studied the cyclisations of allylsilane **20** and phenylsilane **22** — prepared in analogous fashion to the trimethylsilyl-substituted ketones **8** and **9**.

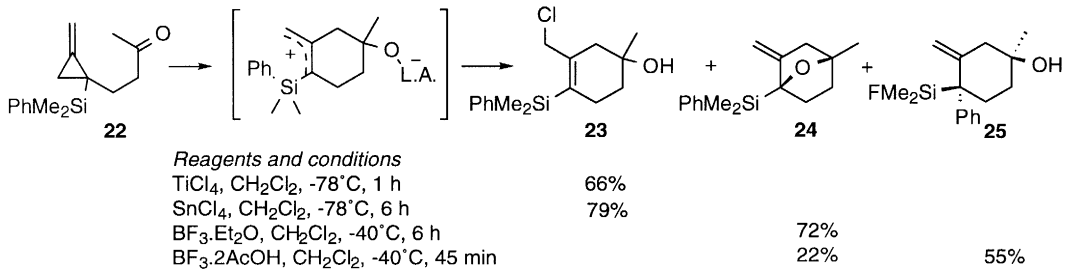
Treatment of allylsilane **20** with $TiCl_4$ or $SnCl_4$ did not lead to any isolable cyclised products. Treatment with either $BF_3 \cdot Et_2O$ or $BF_3 \cdot 2AcOH$, however, gave the silyl fluoride **21**, presumably resulting from intramolecular addition of the allylsilane moiety to the allyl cation intermediate, in moderate yield (Scheme 6).



Scheme 6.

Treatment of phenylsilane **22** with $TiCl_4$ or $SnCl_4$, gave the cyclised allyl chloride **23** in very good yield (Scheme 7), again as a consequence of rapid trapping of the intermediate allyl cation by chloride, and treatment of **22** with $BF_3 \cdot Et_2O$ gave the bicyclic ether **24**, also in very good yield, analogous to reaction of the trimethylsilyl-substituted methylenecyclopropyl ketone **8** (Scheme 3). Treatment of phenylsilane **22** with $BF_3 \cdot 2AcOH$, however, did now lead to silylfluoride **25**, as a single diastereoisomer as shown,[8] and in reasonable yield, accompanied by bicyclic ether **24**. Clearly under these conditions the phenyl transfer from silicon to the allyl cation can compete with intramolecular trapping by the alkoxide nucleophile.

In conclusion, silylated methylenecyclopropyl ketones have proved to be more reactive than the non-silylated analogues, and cyclise under relatively mild conditions to give six- and seven-membered ring products in good yields. The mild conditions used also allow the allyl cation, formed as an intermediate in the cyclisation, to be trapped in further carbon–carbon bond-forming reactions, as exemplified by the reactions of allylsilane **20** and phenylsilane **22**.



Scheme 7.

Acknowledgements

We thank SmithKline Beecham for supporting this work and Thomas Gelbrich for help in determining the stereochemistry of **14** and of **25**.

References

1. Peron, G. L. N.; Kitteringham, J.; Kilburn, J. D. *Tetrahedron Lett*. **1999**, *40*, 3045.
2. The mechanism was first proposed by Hosomi et al. who described the Lewis acid mediated intermolecular addition of methylenecyclopropanes to ketones and aldehydes: Miura, K.; Takasumi, M.; Hondo, T.; Saito, H.; Hosomi, A. *Tetrahedron Lett*. **1997**, *38*, 4587.
3. Hosomi et al. reported that 2-trimethylsilylmethylenecyclopropane was considerably more reactive than simple methylenecyclopropane in their study on intermolecular additions to ketones and aldehydes; see Ref. 2.
4. For the original preparation of 2-trimethylsilylmethylenecyclopropane and further alkylation reactions, see: Sternberg, E.; Binger, P. *Tetrahedron Lett*. **1985**, *26*, 301.
5. For the original description of this one-pot procedure, see Ref. 4. See also: Thomas, E. W. *Tetrahedron Lett*. **1983**, *24*, 1467.
6. All new compounds were characterised by IR, MS, ^{1}H and ^{13}C NMR, with ^{1}H–^{1}H and ^{1}H–^{13}C correlation spectra, where necessary, to aid the assignments, and by HRMS. Full details will be reported in due course.
7. The conversion of **8** to **12** is essentially a [3+2] cycloaddition of a silylated trimethylenemethane (TMM) equivalent to a ketone. The use of methylenecyclopropanes as TMM equivalents in [3+2] cycloaddition reactions with olefins, using transition metal catalysis, is well-documented: (a) Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 98; (b) Lewis, R. T.; Motherwell, W. B.; Shipman, M.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron* **1995**, *51*, 3289; (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.
8. The stereochemistry of **14** and **25** was determined by X-ray crystallographical analysis. Full details will be published in due course.