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Lewis Acid Mediated Cyclisation of Methylenecyclopropyl Ketones and Aldehydes

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Abstract

The Lewis acid mediated cyclisation of various methylenecyclopropyl ketones, ketals and aldehydes has been investigated as a new route to six- and seven-membered rings. Cyclisation of aldehyde **6**, ketal **9** and ketone **11** with $TiCl_4$ gave cyclohexene products, and cyclisation of ketal **10** gave a dichlorocycloheptene, all *via* nucleophilic addition of the methylenecyclopropyl π bond to the activated carbonyl. Cyclisation of ketone **12**, however, with $SnCl_4$, gave a cyclopentanol **21**, presumably *via* nucleophilic addition of a cyclopropyl σ bond to the activated carbonyl.

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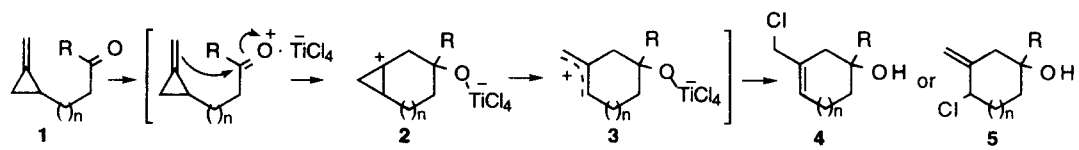
Methylenecyclopropane derivatives have been extensively used in synthesis, for example in [3+2] cycloaddition reactions catalysed by transition metals,[1] in radical based annulation reactions[2] and in radical cyclisation reactions.[3] A recent report by Hosomi *et al.* showed that methylenecyclopropane could be also coupled with carbonyl compounds using Lewis acids such as $TiCl_4$.[4] We have investigated the analogous intramolecular cyclisation of methylenecyclopropyl ketones and aldehydes and we wish to report our results in this paper.[5] Activation of aldehyde or ketone **1**, with a suitable Lewis acid such as $TiCl_4$, should allow intramolecular nucleophilic attack of the double bond of the methylenecyclopropyl unit leading to cyclohexyl cation **2**, which, by analogy with the mechanism proposed by Hosomi,[4] should open to give π-allyl cation intermediate **3**, which in turn, can be quenched by a chloride anion to give cycloalkene **4** or methylenecycloalkane **5** (Scheme 1).



1 2 3 4 5

Scheme 1

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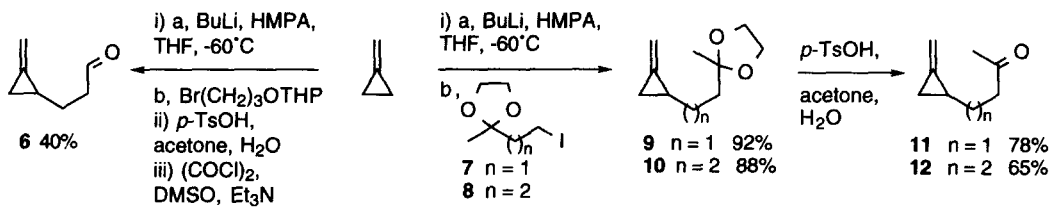
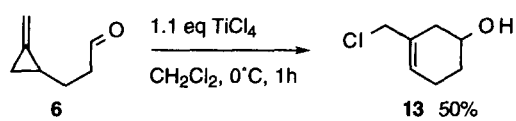
Since methylenecyclopropyl ketones and aldehydes such as **1** can be readily prepared by alkylation of lithiated methylenecyclopropane,[6] this, in conjunction with the successful realisation of the cyclisation (Scheme 1) would provide a novel and simple sequence for the preparation of cycloalkanes or cycloalkenes.

The substrates we initially chose to study were aldehyde **6** and ketones **11** and **12**. Alkylation of lithiated methylenecyclopropane, in the presence of HMPA, with tetrahydropyranyl protected 3-bromopropan-1-ol, deprotection of the resulting tetrahydropyranyl ether with *p*-TsOH in wet acetone, and Swern oxidation gave aldehyde **6** (Scheme 2). Similarly, alkylation of lithiated methylenecyclopropane, in the presence of HMPA, with iodides **7** or **8** followed by deprotection of the resulting ketals **9** and **10**, with *p*-TsOH in wet acetone, gave ketones **11** and **12**.



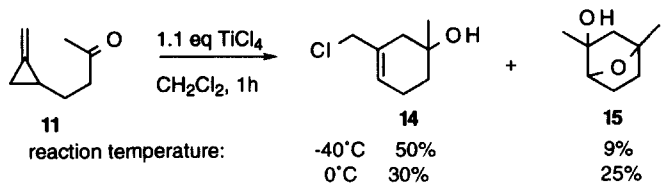
Scheme 2

Cyclisation of aldehyde **6** was investigated first, using a range of Lewis acids. In common with Hosomi, we found that $TiCl_4$ worked best for aldehyde **6**, giving a 50% yield of cyclohexene **13** as the only isolated product[7] when the reaction was conducted at 0 °C (Scheme 3). Lower yields of **13** were obtained when the reaction was carried out at either higher or lower temperatures. With $SnCl_4$ (at -78 °C) a low yield (7%) of cyclohexene **13** was obtained, whereas treatment of aldehyde **6** with $BF_3.Et_2O$ gave a complex mixture of products, and no reaction was observed using $ZnCl_2$.



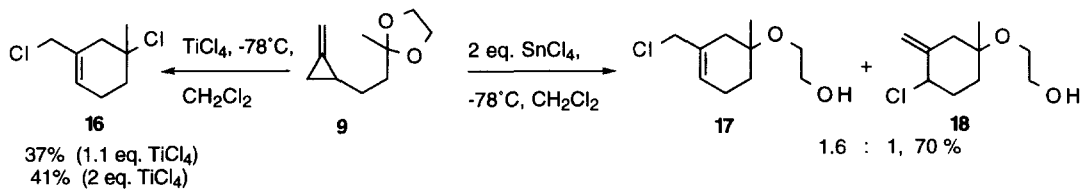
Scheme 3

A similar range of Lewis acids were investigated for the cyclisation of ketone **11**. Again, using $TiCl_4$, a reasonable yield of cyclised product **14** was obtained by conducting the reaction at -40 °C (Scheme 4). At higher temperatures, an increasing amount of byproduct **15** was formed (as a single diastereoisomer[8]), presumably by intramolecular trapping of the intermediate allyl cation by the alkoxide, and subsequent hydration of the double bond. With $SnCl_4$, at -78 °C, a low yield (6%) of cyclohexene **14** was obtained, whereas treatment of ketone **11** with $BF_3.Et_2O$ only ever gave a complex mixture of products, and no reaction was observed with $ZnBr_2$, HCl, Et_2AlCl or $EtAlCl_2$.



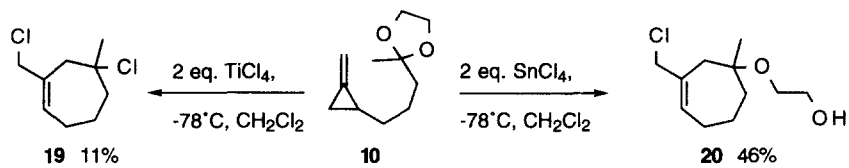
Scheme 4

Lewis acid mediated cyclisation of ketal **9** was also investigated (Scheme 5). Ketal **9**, upon treatment with 1.1 eq. $TiCl_4$, at - 78 °C, gave dichloride **16** in 37% yield. Using 2 eq. $TiCl_4$, a slightly improved yield of **16** was obtained (41%). Using 2 eq. $SnCl_4$, cyclohexene **17** and methylene cyclohexane **18** (as a single diastereoisomer[8]) were obtained as an inseparable mixture, in a 1.6 : 1 ratio, in 70% yield.



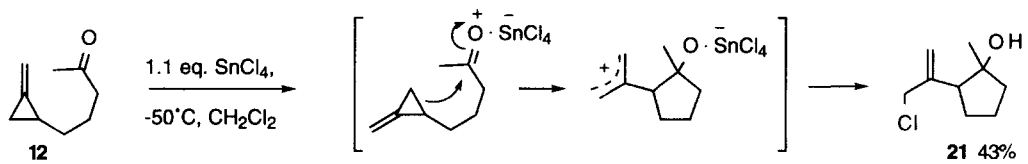
Scheme 5

Similar results were obtained from the cyclisation of ketal **10** (Scheme 6). Thus a dichloride **19** was obtained in 11% yield when the cyclisation was carried out with 2 eq. $TiCl_4$, but using 2 eq. $SnCl_4$, gave cycloheptene **20** in 46% yield, and as a single regioisomer.



Scheme 6

The reaction of ketone **12** with Lewis acids, however, did not give the expected cycloheptene. Instead, cyclisation using 1.1 eq. $SnCl_4$, at -50°C, gave cyclopentanol **21** in 43% yield, and as a single diastereoisomer[8] (Scheme 7).



Scheme 7

Presumably **21** is formed *via* nucleophilic addition of the 'distal' cyclopropyl σ bond to the activated carbonyl. Electrophilic addition to cyclopropanes is well known[9] and is presumably preferred, in this case, to addition to the double bond of the methylenecyclopropyl because of favourable orbital overlap in the transition state, although why this should be is not clear and merits further investigation. Using $BF_3.Et_2O$ or $TiCl_4$ for the cyclisation of **12** gave a complex mixture of inseparable products and there was no reaction with HCl, Et_2AlCl or $EtAlCl_2$.

In conclusion, we have found that cyclisation of methylenecyclopropane derivatives using Lewis acids provides a novel route to six- and seven-membered rings. The efficiency of these cyclisations is sensitive to the Lewis acid used, but under optimum conditions gave reasonable yields of highly functionalised products.

Acknowledgements

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7. All new compounds were characterised by IR, MS, ^1H and ^{13}C NMR, with ^1H-^1H and ^1H-^{13}C correlation spectra, where necessary, to aid the assignments, and by HRMS. Full details will be reported in due course.
8. The stereochemistry of this compound has not yet been determined.
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