## Double Ring-Opening Reactions of Bis-Cyclopropanes Promoted by Iron Salts

Me<sub>3</sub>SiO

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Abstract: Certain bis-cyclopropanes were prepared from the corresponding dienol silane and, on treatment with ferric salts, were found to undergo two sequential C-C bond cleavages to give products corresponding to overall two carbon ring-expansion. In one case the nature of the product obtained was found to depend upon the types of ferric salts employed.

Key words: cyclopropane, ring expansion, iron salts

Scheme 2 A protocol for overall ring expansion of a cyclic ketone by

one carbon was described by Saegusa and co-workers in 1976.<sup>1</sup> Initial enol silane formation and cyclopropanation serves to convert a ketone such as cyclohexanone 1 into the corresponding silyloxycyclopropane 2, which is then treated with FeCl<sub>3</sub> in DMF to effect C-C bond cleavage to give 3, Scheme 1.



Scheme 1

The key reaction is thought to involve single electron transfer from the cyclopropane to FeCl<sub>3</sub>, thus generating a ring-expanded carbon-centred radical that reacts with further  $FeCl_3$  to install the chlorine atom in the product. The initially formed B-chloroketone normally undergoes facile elimination of HCl to give the corresponding  $\alpha,\beta$ -unsaturated ketone.

Recently this reaction has been developed and extended by Booker-Milburn,<sup>2</sup> who has demonstrated the utility of alternative iron salts in the reaction (see later),<sup>3</sup> applied the reaction to alternative types of substrate,<sup>4</sup> and has shown that the carbon-centred radical resulting from the C-C bond cleavage can be cyclised onto pendant unsaturated side-chains.5

A crucial aspect of the reaction is the observed preference for cleavage of the endocyclic cyclopropane C-C bond, which contrasts with the stereoelectronically controlled exocyclic bond cleavage observed in many related examples involving cyclopropylcarbinyl radicals.<sup>6</sup> We were intrigued by the prospect of extending this reaction to biscyclopropanes, as outlined in Scheme 2, and describe herein our preliminary results in this area.



MeaSi

5

tex

FeCl<sub>3</sub>

DMF

6

This approach appeared particularly attractive, bearing in mind the availability of six-membered starting materials and the prospect of their conversion into eight-membered carbocycles or heterocycles.9 In fact, to date we have explored only *bis*-cyclopropane substrates -  $5 (X = CH_2)$ .<sup>10</sup>

Preparation of two suitable bis-cyclopropanes fused to six-membered systems was achieved as indicated in Scheme 3.<sup>11</sup>





In our hands, access to 8 free from minor regioisomeric impurities was best achieved by silvlation of the  $\beta$ ,  $\gamma$ -unsaturated cyclohexanone, which is available by controlled hydrolysis of the vinyl ether 7.12 Double cyclopropanation to give 9 as a single diastereoisomer was accomplished by

the Furukawa procedure using the modified conditions described by Denmark.<sup>13</sup> Worries concerning the volatility of intermediates and products prompted us to prepare a more highly substituted substrate **12**, starting with enone **10**. In this case, adequate purification of the final *bis*-cyclopropane could only be achieved following desilylation and, since such cyclopropanols are known to participate in Saegusa-type reactions,<sup>14</sup> we used **12** without recourse to re-silylation.

Reaction of either **9** or **12** under typical Saegusa conditions, or under the modified conditions described by Booker-Milburn, gave the products **13** and **14** respectively, as shown below.<sup>15</sup>



A:  $Fe(NO_3)_3$ ; B:  $FeCI_3$ ; C:  $Fe(NO_3)_3 + NCS$ ; D:  $Fe(NO_3)_3 + (PhS)_2$  \* complex mixture obtained

Pleasingly, the anticipated eight-membered  $\beta$ , $\gamma$ -unsaturated ketones were formed as we had planned, although our success in achieving the double ring cleavage process to access these substituted cyclooctenones was tempered by the moderate yields obtained. In the case of **13** (X = H or Cl) this was in part due to volatility, but separation of products from uncharacterised byproducts was also a problem.

We went on to consider a larger ring system **15**, which was readily prepared from cyclooctadiene, Scheme 4.<sup>16</sup>



## Scheme 4

This system gave a remarkable outcome in that changing the nature of the iron salt resulted in a dramatic change in the type of product observed. Using  $Fe(NO_3)_3$  alone we obtained the decalin **16** as a mixture of diastereomers (*ca.* 2:1 ratio),<sup>17</sup> whereas with FeCl<sub>3</sub> or combinations of Fe(NO<sub>3</sub>)<sub>3</sub> with NCS or diphenyldisulfide we obtained the ten-membered ring ketones **17** or **18** (both as exclusively the *E*-isomer).<sup>18</sup> In the latter cases the product is presumably the result of very rapid radical trapping, whereas when  $Fe(NO_3)_3$  is employed alone the intermediate homoallylic radical is quenched (by hydrogen atom abstraction from the solvent) more slowly, allowing time for C=C isomerisation and transannular ring closure onto the ketone function.

The results in Scheme 4 also allow us to make other, albeit preliminary observations. Firstly, in line with the observations of Booker-Milburn, the  $Fe(NO_3)_3$  systems seem to give improved results compared to the original Saegusa protocol. Secondly, the results for **15** are significantly improved compared to the smaller ring sized systems **9** and **12**. This may be due to the more flexible nature of the larger ring allowing for better bond alignment for endocyclic bond cleavage in intermediate radicals, which results in more efficient channelling of intermediates towards a single product.

In conclusion, we have demonstrated for the first time the viability of a two carbon ring expansion protocol which utilises iron-mediated bond cleavage reactions of *bis*-cy-clopropanes. The results provide further evidence of the utility of the Booker-Milburn variants of the Saegusa reaction as well as highlighting, in one case, a remarkable product dependency on the nature of the iron salt employed.

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## **References and Notes**

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- (15) Representative experimental procedure 14 (X = SPh) from 12.

A solution of dried ferric nitrate was prepared by stirring a solution of  $Fe(NO_3)_3.9H_2O$  (0.89g, 2.2 mmol) in dry DMF (10 ml) over 4Å molecular sieves under an atmosphere of argon, for 16h. This solution was then added via syringe pump, over a period of 30min, to a solution of **12** (0.23g, 1.0 mmol) and PhSSPh (0.65g, 3.0 mmol) in dry de-gassed DMF (5 ml). The mixture was stirred until TLC showed complete consumption of starting material (1.5h). The reaction mixture was then poured into water (100 ml) and the product extracted into EtOAc (3 x 50 ml). The organic extract was dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to give the crude product as a yellow solid. This material was purified by flash chromatogra-

phy (5% Et<sub>2</sub>O in petroleum ether) to give **14** as a white solid (193 mg, 57%), m.p. 133–134°C (from cyclohexane)  $v_{max}$ / cm<sup>-1</sup> (CHCl<sub>3</sub>) 1689;  $\delta_{\rm H}$  (400 MHz;CDCl<sub>3</sub>) 1.19 (3H, s, CH<sub>3</sub>), 1.22 (3H, s, CH<sub>3</sub>) 1.95 (1H, dd, *J* 4 and 12, 3-H), 2.39 (1H, dd, *J* 12 and 14, 3-H), 2.73 (2H, app.d, *J* 5, 5-H), 3.16 (1H, dd, *J* 5 and 16, 8-H), 3.60 (1H, ddd, *J* 4, 4, 4 and 14, 4-H), 3.70 (1H, dd, *J* 5 and 16, 8-H), 5.80 (1H, dd, *J* 5 and 5, 7-H), 6.95–6.99 (2H, m, Ar-H) and 7.13-7.28 (8H, m, Ar-H);  $\delta_{\rm C}$  (100 MHz; CDCl<sub>3</sub>) 22.8 (CH<sub>3</sub>), 29.0 (CH<sub>3</sub>), 31.9 (5-CH<sub>2</sub>), 42.3 (8-CH<sub>2</sub>), 42.4 (3-CH<sub>2</sub>), 46.3 (4-CH), 48.1 (2-C), 125.1 (7-CH), 126.7 (CH), 126.8 (CH), 126.9 (CH), 128.1 (CH), 128.7 (CH), 132.0 (CH), 134.7 (C), 137.5 (C), 144.8 (C) and 216.3 (1-C); *m/z* (Found: *M*+*Na*<sup>+</sup>359.1423.C<sub>22</sub>H<sub>23</sub>OS requires *M*+*Na*, 359.1446).

- (16) Compound 15 was prepared from cyclooctadiene by the following sequence of reactions: (i) MeCO<sub>3</sub>H, Na<sub>2</sub>CO<sub>3</sub>; (ii) LiAlH<sub>4</sub> (57% two steps); (iii) TPAP, NMO (55%); (iv) LDA, Me<sub>3</sub>SiCl (76%); (v) Et<sub>2</sub>Zn, ClCH<sub>2</sub>I (77%).
- (17) Both diastereomers show O–H str. in the IR but no C=O absorption and no carbonyl in the <sup>13</sup>C NMR. For the major, lesspolar, isomer (Found:  $M^+$ , 152.1201. C<sub>10</sub>H<sub>16</sub>O requires *M*, 152.1202).
- (18) The structure of **17** was confirmed by X-ray crystallography; full details will be reported elsewhere.