Tetrahedron Letters, Vol.27, No.8, pp 971-974, 1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

TANDEM ELECTROCYCLIC-SIGMATROPIC REACTION OF BENZOCYCLOBUTENES. 2[1]. A NEW ROUTE TO ISOCHROMAN-3-ONE-4-SPIRO-1'-CYCLOALK-3'-ENES

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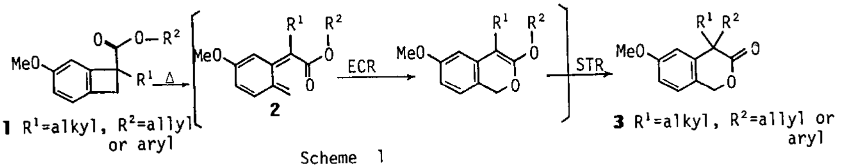
Summary: Thermolyses of the benzocyclobutenylspirolactones, easily derived from 1-cyano-5-methoxybenzocyclobutene, afforded isochroman-3-one-4-spiro-1'-cycloalk-3'-enes in good yields *via* tandem electrocyclic-sigmatropic reaction of *o*-quinodimethane.

We recently reported[1] the tandem electrocyclic(ECR)-sigmatropic reaction(STR) of the *o*-quinodimethane (**2**), generated *in situ* by thermolysis of the benzocyclobutenes (**1**), and established an expedient route to 4,4-disubstituted isochromanones (**3**). (Scheme 1)

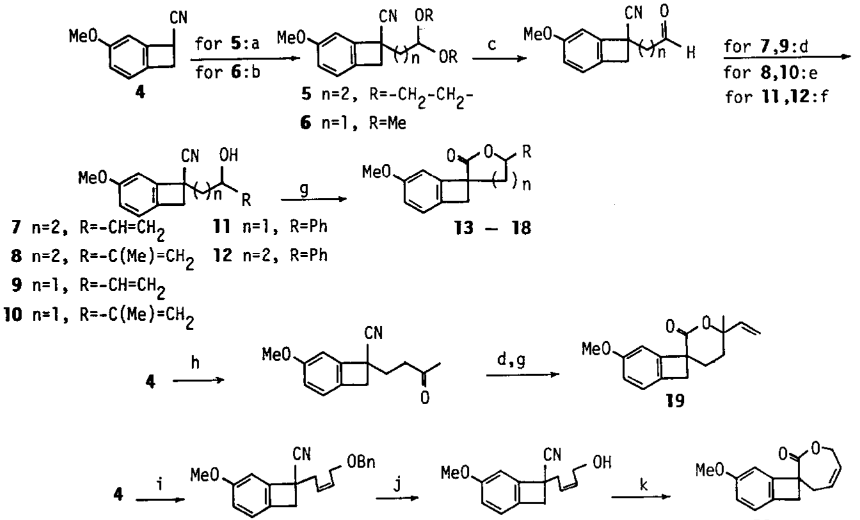


Scheme 1

We report here the extension of this methodology to the synthesis of isochroman-3-one-4-spiro-1'-cycloalk-3'-enes by thermolyses of benzocyclobutenylspirolactones, which is a cyclic version of the reported methodology and seems to provide an efficient route to a synthon for natural products such as Amaryllidaceae alkaloids[2].

The required substrates for thermolyses were synthesized from readily available 1-cyano-5-methoxybenzocyclobutene (**4**)[3] as outlined in Scheme 2.

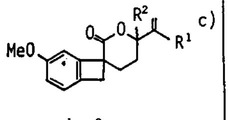
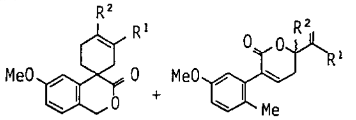
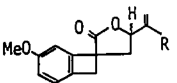
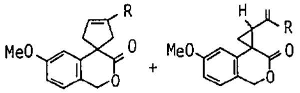
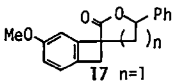
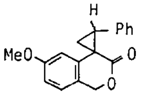
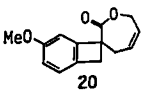
Alkylation of **4** with 2-(2-bromoethyl)-1,3-dioxolane utilizing LDA as a base followed by acid hydrolysis of the resulting acetal (**5**) gave the corresponding aldehyde, which was then reacted with vinylmagnesium bromide to give **7** as a mixture of diastereomers. Basic hydrolysis of **7** and acid treatment of the resulting hydroxycarboxylic acid provided the spirolactone (**13**) as a diastereomeric mixture in ca. 50 % overall yield. The preparation of the



a) Br, LDA, HMPA b) Br OMe OMe, LDA, HMPA c) H_3O^+ d) MgBr e) MgBr f) PhMgBr
g) KOH, aq.EtOH then p-TsOH, CH_2Cl_2 h) MVK, LDA, HMPA i) Br OBn, LDA, HMPA
j) $BF_3\cdot OEt$, Me_2S k) KOH, aq.EtOH then p-TsOH, PhH, with Dean-Stark, reflux

Scheme 2

Table

Entry	substrate	a) Time(h)	Product	Yield(%)
1 2 3	 c) 13 $R^1=R^2=H$ 14 $R^1=Me$, $R^2=H$ 19 $R^1=H$, $R^2=Me$	1.5 1.5 2	 21 $R^1=R^2=H$ 14:1 24 $R^1=R^2=H$ 22 $R^1=Me$, $R^2=H$ 17:1 25 $R^1=Me$, $R^2=H$ 23 $R^1=H$, $R^2=Me$ 11:1 26 $R^1=H$, $R^2=Me$	89 99 b) 88
4 5	 15 R=H 16 R=Me	1.5 2	 27 R=H 2:3 29 R=H 28 R=Me inseparable 30 R=Me	80 80 b)
6 7	 17 n=1 18 n=2	3.5 1	 31 decomposed during work-up	81 b)
8	 20	7.5	27	78

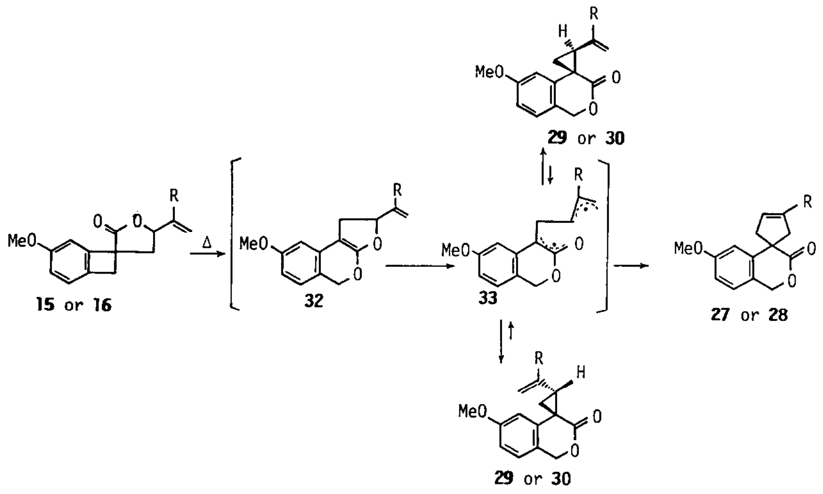
a) Time of heating at 180°C in o-dichlorobenzene(degassed) under on atmosphere of argon
b) Based on the consumed starting material
c) Waved line in the structures indicats a mixture of diastereomers

other substrates was carried out analogously to that of **13**.

The thermolyses (Table) were typically carried out in a 0.03-0.05M *o*-dichlorobenzene (ODB) solution at a bath temperature of 180°C under an atmosphere of argon. The progress of the reaction was monitored by TLC analysis.

On heating of the δ-lactone (**13**), from which Ireland-Danishefsky[4] type [3,3]STR would be expected, two products were obtained in a ratio of 14 : 1 in 89 % yield. The major product was the expected isochroman-3-one-4-spiro-1'-cyclohex-3'-ene (**21**)[5] *via* tandem ECR-[3,3]STR and the minor one was characterized spectroscopically as **24** *via* [1,5]STR of the E-*o*-quinodimethane. Other δ-lactones (Entries 2 and 3) also resulted in the same type of products as in the case of **13**.

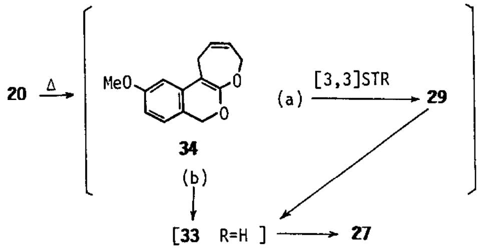
In the case of the γ-lactone (Entry 4), on the other hand, the spirocyclopentene (**27**) and the spirovinylcyclopropane (**29**), (as a diastereomeric mixture), were obtained in a ratio of 2 : 3 in 80 % yield. The structure of **29** was deduced from its ^{1}H and ^{13}CNMR spectram and supported by the following chemical reaction. Thus, on heating a solution of **29** in ODB for 7.5 h, **29** was cleanly converted to **27** by thermal vinylcyclopropane-cyclopentene rearrangement.[6,7] The inseparable mixture of **28** and **30** (Entry 5) was also converted to **28** for 3 h by the same procedure as above in 82 % yield. From these results, it was suggested that the diradical (**33**)[8] would be an intermediate in the conversion of **15** (or **16**) into **27** (or **28**). (Scheme 3)



Scheme 3

The thermolysis of the phenyl substituted γ-lactone (**17**) gave exclusively the spirocyclopropane (**31**)[9] as a diastereomeric mixture (ca. 3:2 from ^{1}HNMR) in 81 % yield, apparently arising from radical scission-recombination process of the ketene acetal intermediate as indicated above. In the case of a six-membered version of **17** (Entry 7), although the thermolysis proceeded cleanly, the product(s) could not be isolated because of the rapid decomposition.

Finally we also examined the thermolysis of the seven-membered spirolactone with endo-cyclic olefin, such as **20**, comparable with the Funk's variation[10] of [3,3]STR. It took 7.5 h and gave a single product, the spirocyclopentene (**27**) which was identical with the sample prepared in Entry 4, presumably arising from the path (a) [**34**→**29**→ **33**] or the direct path (b) [**34** → **33**] in Scheme 4.



Scheme 4

In conclusion , the chemistry described here provides a unique and useful synthetic methodology for constructing spiro-fused isochroman-3-one derivatives.

Applications in Amaryllidaceae alkaloids synthesis are underway.

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(Received in Japan 24 December 1985)