Pergamon

Tetrahedron Letters 40 (1999) 1075–1078

TETRAHEDRON LETTERS

4+3 Cycloaddition Reactions of Halogen-Substituted Cyclohexenyl Oxyallylic Cations

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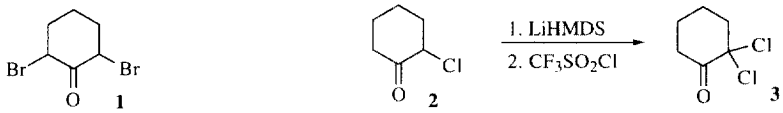
Received 5 May 1998 ; accepted 4 December 1998

Summary: 2,6-Dibromo- and 2,2-dichlorocyclohexanone react with base in the presence of various dienes to give 4+3 cycloadducts in fair to good yields. Preliminary studies of the cycloadducts suggest that they are unstable and are recalcitrant to nucleophilic addition and cross-metathesis. However, the LAH reduction products undergo a quasi-Favorskii rearrangement upon treatment with potassium hydride and one cycloadduct derivative was dehalogenated using radical chemistry.

The 4+3 cycloaddition reaction represents a powerful process for the synthesis of seven-membered and even larger rings.[1] As part of our continuing studies of both the inter- and intramolecular variants of this reaction,[2] we have begun a study of cyclic, halogen-substituted, oxyallylic cations in anticipation of developing methods for easy access to polycyclic molecules bearing a bridgehead halogen. There is a great deal of useful synthetic chemistry associated with such systems.[3] While both halogen-substituted, and cyclic, allylic and oxyallylic cations have been examined in the context of 4+3 cycloaddition,[4,5] to the best of our knowledge, there is no study of the cycloaddition of intermediates in which both of these structural features are combined.

This report details progress on our initial studies involving cyclohexenyl oxyallylic species. The starting materials were 2,6-dibromocyclohexanone **1** and 2,2-dichlorocyclohexanone **3**. We prepared the former by



Equation 1

known methods[6] and the latter by chlorination of the corresponding enolate (equation 1).[7] Preliminary optimization studies were conducted with **1** and furan. A summary of some cycloaddition results as a function of reaction conditions is shown in Table 1. The best yields were obtained using trifluoroethanol or a 1:1 mixture of ether and trifluoroethanol as solvent and allowing the reaction mixture to warm slowly from -78 °C to room temperature. The latter solvent mixture was found more useful for low temperature work. An excess of diene was typically needed to obtain acceptable yields. Entries 5 and 7-8 suggest that large excesses of diene would be generally suitable, but such an approach is ultimately not satisfactory, especially for valuable dienes. This is a general difficulty with many intermolecular 4+3 cycladditions and a good general solution remains to be found.

With the preliminary optimization data in hand, we decided to explore the generality of the reaction. These results are summarized in Table 2. These reactions were run in 1:1 TFE/Et_2O in the presence of excess diene (10 eq.) and 3 equivalents of triethylamine. Reactions were begun at -78 °C but allowed to warm and stir at room temperature for up to 24 hours. In general, the cycloadducts obtained from this reaction are unstable as solids or neat liquids and need to be reduced at the carbonyl or olefin to afford products which can be conveniently

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PII: S0040-4039(98)02629-X

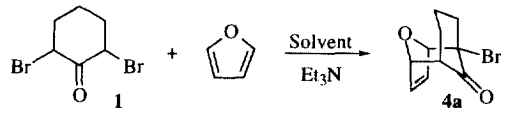


Table 1. The Reaction of 1 with Furan.

Entry	Solvent	Eq. Diene	Eq. Et_3N	[1], M[b]	T °C	Time[c]	Yield(%)[d]
1	$Et_2O/LiClO_4$[a]	200	2.6	0.23	rt	2.75 h	18
2	TFE/THF (1:1)	8.6	2.6	0.11	-78 to 0	90 m	21
3	furan	85	2.7	0.16	-78 to 0	110 m	low[e]
4	furan/TFE (6:1)	54	2.6	0.22	-78 to 0	120 m	20
5	TFE/Et_2O (1:1)	8.5	2.6	0.11	-78 to 0	95 m	35
6	TFE	7	2	0.10	rt	45 m	48
7	TFE/Et_2O (1:1)	50	2.7	0.11	-78 to rt	4 d	43
8	TFE/Et_2O (1:1)	75	2.6	0.12	-78 to rt	7 d	58

[a]3.7 M in $LiClO_4$. [b]The concentration was calculated using solvent only, even if large amounts of furan were present. [c]Time of the reaction from start to quench; h = hours, m = minutes, d = days [d]Yield after chromatographic purification. [e]TLC indicated very little conversion to product.

characterized. However, all cycloadducts are sufficiently stable for chromatographic purification and for NMR data to be obtained. As can be seen, the yields for the cycloaddition/reduction sequence are fair to good.

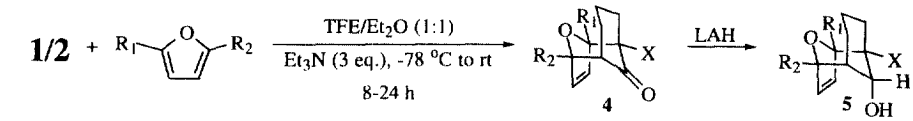


Table 2. The Reaction of 1 and 2 with Various Dienes.

Entry	Ketone	R_1	R_2	X	Product	Yield(%)[a]	Product	Yield(%)[b]	Overall Yield(%)[c]
1	**1**	H	H	Br	**4a**	d	**5a**	d	40[e]
2	**1**	Me	H	Br	**4b**	d	**5b**	d	51
3	**1**	Me	Me	Br	**4c**	d	**5c**	d	62
4	**1**	$-CH_2OTBS$	H	Br	**4d**	31	**5d**	58	18
5	**1**	$-(CH_2)_3OTBS$	H	Br	**4e**	66	**5e**	73	48
6	**2**	H	H	Cl	**4f**	31	**5f**	43	13
7	**2**	Me	H	Cl	**4g**	63	**5g**	80	50
8	**2**	Me	Me	Cl	**4h**	74	**5h**	83	61

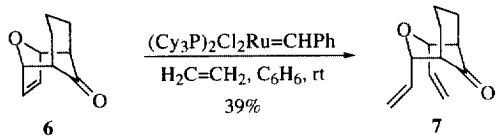
[a]Yield for cycloaddition after chromatographic purification. [b]Yield for reduction after chromatographic purification. [c]Combined yield for both steps after chromatographic purification. [d]Yield not recorded. [e]Fifty equivalents of furan was used.

The data suggest that the cycloaddition improves as alkyl substitution on the furan ring increases. The limit of this effect has not been tested. It appears that the cycloaddition is also highly regioselective. Reactions with 2-substituted furans proceeded to produce single cycloadducts, in which the alkyl appendage and the halogen were disposed syn to each other (Table 2, entries 2, 4, 5 and 7). The assignment of structure in these cases was made on the basis of an X-ray crystal structure of **4b** which showed the syn relationship between the methyl and bromine substitutents. Other structures were assigned accordingly.

Such regioselectivity has precedent in the 4+3 cycloaddition reactions of acyclic, halogenated oxyallyls.[8] The exact mechanistic interpretation of this result must await further experimentation. However, one possible rationalization involves a stepwise mechanism in which the most stable zwitterion is produced. This zwitterion then collapses to product.

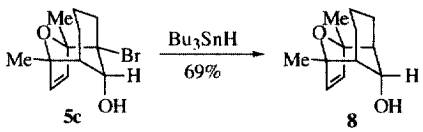
To date we have been unable to effect cycloaddition to cyclopentadiene with either **1** or **2** in anything but low yield. In addition, cycloadditions with 2-methoxyfuran, 2-phenylfuran and cyclohexadiene have been unsuccessful. Simple solvolysis of the dihaloketones and electrophilic substitution are complicating features with these dienes under the conditions of the reaction. Work to develop cyclic, halogenated oxyallyls which will productively react with these dienes continues.

In an effort to explore the utility of the cycloadducts, some of their chemistry was explored. It is noteworthy that we have only been able to achieve addition to the carbonyl of the cycloadducts using LAH. Other nucleophiles including vinylmagnesium bromide, dilithiomethylphenyl sulfone and methyllithium gave only starting materials upon attempted reaction with **4a**.



6 **7**

Equation 2

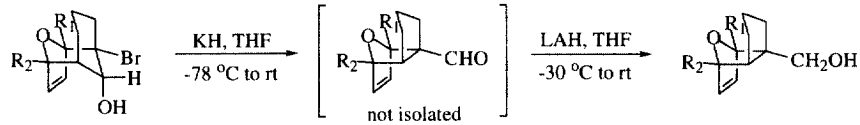


5c **8**

Equation 3

We also found that these products were recalcitrant to cross-metathesis.[9] While **6** gave a cross-metathesis product with ethylene (39% unoptimized, equation 2) and the Grubbs' catalyst, **4a** did not react under a number of different conditions.

More promising was chemistry involving the halogen. We were able to show that radical reduction of **5c** produced the alcohol **8** in 69% yield (equation 3).[10] More creative trapping of the intermediate radical has not yet been performed.[11] Interestingly, treatment of some of the reduction products with potassium hydride resulted in a quasi-Favorskii rearrangement to produce aldehydes which were reduced in situ with LAH to produce the corresponding alcohols.[12] These results are summarized in equation 4. The in situ reduction was carried out because of the apparent instability of the aldehydes resulting from the quasi-Favorskii rearrangement.



5a: $R_1 = R_2 = H$
5b: R_1 = Me, $R_2 = H$
5c: $R_1 = R_2$ = Me
5d: $R_1 = CH_2OTBS$, $R_2 = H$
5e: $R_1 = -(CH_2)_3OTBS$, $R_2 = H$

9a: $R_1 = R_2 = H$; 61%
9b: R_1 = Me, $R_2 = H$; 68%
9c: $R_1 = R_2$ = Me; 73%
9d: $R_1 = CH_2OH$, $R_2 = H$; 54%
9e: $R_1 = -(CH_2)_3OTBS$, $R_2 = H$; 83%

Equation 4

Note that the protecting group is lost from **5d** during the reaction sequence. These compounds are formally Diels-Alder cycloadducts of furan, though to our knowledge such structures (i.e., furan/cyclopentene carboxaldehyde adducts) have not been prepared. Our attempts to prepare a Diels-Alder adduct of cyclopentene carboxaldehyde and furan, 2-methylfuran or 2,5-dimethylfuran have failed under thermal conditions and in the presence of a Lewis acid.

The chemistry described herein offers rapid access to complex polycyclic structures in a stereoselective and regioselective fashion. The combination of a 4+3 cycloaddition/quasi-Favorskii reaction makes halogen-substituted oxyallylic cations synthetic equivalents of cyclopentene carboxaldehydes. At least in some cases, this allows access to Diels-Alder cycloadducts which could not be prepared directly using a more direct 4+2 cycloaddition approach. Further development of this methodology and exploration of the bridgehead halide reactivity of these systems is in progress and results will be reported in due course.[13,14]

Acknowledgements: This work was supported by the National Science Foundation. MH thanks the Alexander von Humboldt Foundation for a fellowship and Professors Reinhard Brückner (then Göttingen, now Freiburg) and Lutz F. Tietze (Göttingen) for their hospitality. We thank the National Science Foundation for partial support of the NMR (PCM-8115599) facility at the University of Missouri-Columbia and for partial funding for the purchase of a 500 MHz spectrometer (CHE-89-08304) and an X-ray diffractometer (CHE-90-11804).

Reference and Notes

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13. Compounds **4d**, **5a-h**, **8** and **9a-e** exhibited satisfactory ^{1}H and ^{13}C NMR and IR spectral data as well as satisfactory combustion analysis or high resolution exact mass data.
14. Representative experimental procedures. Synthesis of **5c**. 2,6-Dibromocyclohexanone (128 mg, 0.5 mmol) and 0.532 mL of 2,5-dimethylfuran (5 mmol, 10 eq.) were dissolved in a mixture of 2.5 mL of trifluroethanol and 2.5 mL of diethyl ether. The solution was cooled to -78 ^{o}C and stirred under nitrogen. Triethylamine (0.21 mL, 1.5 mmol, 3 eq.) was added dropwise and the mixture was allowed to reach room temperature gradually. After 24 hours at room temperature, the reaction was quenched with 2 mL of water, and extracted with 20 mL of diethyl ether. The organic extracts were washed with 2X4 mL of water, 1X4 mL of brine, and dried over Na_2SO_4. The solvent was removed and column chromatography with hexanes:ethyl acetate (10:1) gave 108 mg of a white solid. This cycloadduct was then treated with 32 mg of LAH (0.80 mmol) in 5.0 mL of THF at room temperature . The mixture was diluted with diethyl ether and quenched with Na_2SO_4-10 H_2O after being stirred at room temperature for 3 hours. The crude product was purified by flash chromatography with hexanes/ethyl acetate (10:1) to give 84 mg of **5c**. Yield: 62%. Synthesis of **9c**. KH (340 mg of 20% susp., 1.7 mmol, 4 eq.) was rinsed 3 times with dry THF. The suspension of this KH in 3 mL of THF was cooled to -78 ^{o}C. Compound **5c** (116 mg, 0.42 mmol) was dissolved in 2.0 mL of THF and the solution was added slowly into the KH/THF suspension. The mixture was allowed to reach room temperature. After 15 minutes at room temperature, the suspension was cooled down to -30 ^{o}C and 67 mg of LAH (1.7 mmol) was added. The mixture was warmed to room temperature slowly. After 1 h at room temperature, the mixture was diluted with diethyl ether and quenched with Na_2SO_4-10 H_2O. The crude product obtained after filtration and removal of solvents was purified by flash chromatography with hexanes/ethyl acetate (4:1 to 2:1) to give 60 mg of **9c** as colorless viscous oil. Yield: 73%.