30. Nucleophilic Addition to C,C Double Bonds. Proximity and Homoconjugative Effects

Preliminary communication[1])

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Summary

Proximity effects alone as well as in combination with electronic effects are responsible for the observed phenomenon of base-catalyzed ether formation initiated by nucleophilic attack on a C,C double bond of the tricyclic olefin alcohols **1**–**10** *(Scheme 1, Table 1)*.

With compounds **1**–**4**, bearing a keto group, formation of the ethers **11**–**14** proceeds through a corresponding homoenolate **b** *(Scheme 2)* as an intermediate. In one case such a species could be trapped as the methyl ether **21** *(Scheme 3)*.

Special attention is given to the stereochemical course of the homoketonization. Ring opening in **21** under acidic conditions occurs regioselectively, however non-stereoselectively *(Scheme 3)*. Full regio- and stereoselectivity (retention) is observed under basic conditions starting from the unsaturated keto alcohols **1** and **2** *(Scheme 4)* as well as from the keto ethers **11** and **12** *(Scheme 5, Table 2)*.

We recently observed base-catalyzed ether formation with polycyclic olefin alcohols [1]. As part of our systematic investigation of this phenomenon[2]) we studied the behaviour of the alcohols **1**–**10**[3]) (see *Scheme 1* and *Table 1*). The results allow us to distinguish two main driving forces: a proximity effect and an electronic effect.

Steric compression is the sole responsible cause for the observed unusual nucleophilic attack on the isolated C,C double bond in **7** (→ **17**), **8** (→ **18**) and **10** (→ **20**). A methyl group at the carbon atom bearing the hydroxyl group enhances the reactivity (compare **2** *vs.* **1**, **4** *vs.* **3**, **6** *vs.* **5**, **8** *vs.* **7**, **10** *vs.* **9**), whereas ring enlargement (X = CH_2–CH_2–CH_2) lowers it (compare **9** *vs.* **7**, **10** *vs.* **8**).

[1]) These results were first presented at the 2nd IUPAC Symposium on Organic Synthesis in Jerusalem/Haifa, September 10–17, 1978 and at the meeting of the Swiss Chemical Society (Schweizerische Chemische Gesellschaft) on October 21, 1978, in Berne.

[2]) The reaction implies nucleophilic attack by the primarily formed alkoxide ion on a C,C double bond bearing no electron-attracting group.

[3]) All new compounds were isolated and their analytical and spectral data are in full agreement with the assigned structures; for **1** and **11** see [2].

Table 1. *Base-catalyzed ether formation starting from olefin alcohols* **1–10**

Transformation[3])	Reaction conditions			Yield
	Base[a])	Temp. °C	Time h	
1→11	A	25	90[b])	quant.
	A	50	8[b])	quant.
	C	25	0.4[b])	quant.
2→12	A	0	2.0[b])	quant.
	A	25	0.12[b])	quant.
	B	25	1.2[b])	quant.
3→13	A	25	340	60%[c])
	A	50	50[b])	quant.
4→14	A	25	2.5[b])	quant.
5→15	A	25	24	–
	A	60	140	60%[d])
6→16	A	25	15[b])	quant.
7→17	A	100	21	–
	C	25	18	–
	C	82	24	50%[e])
8→18	A	25	340	70%[f])
	A	50	190[b])	quant.
	C	25	24[b])	quant.
9→19[g])	A	80	14	–
	C	25	24	–
	C	50	80	–[h])
10→20	A	80	120	5%[i])
	C	25	96	13%[j])

[a]) A: 2N aq. NaOH/CH_3OH 1:1; B: 0.2N aq. NaOH/CH_3OH 1:1; C: 1 molal *t*-BuOK/*t*-BuOH; [b]) Determined by TLC; [c]) In addition to 30% starting material; [d]) In addition to 10% starting material; [e]) In addition to 30% of the ketone resulting from oxidation of alcohol **7**; [f]) In addition to 30% starting material (determined by ^{1}H-NMR.); [g]) **19** can easily be prepared from **9** by hydroxymercuration followed by $NaBH_4$-reduction; [h]) In addition to 60% starting material the sole isolated compound (30%) is the ketone resulting from oxidation of alcohol **9**; [i]) In addition to 90% starting material; [j]) In addition to 75% starting material.

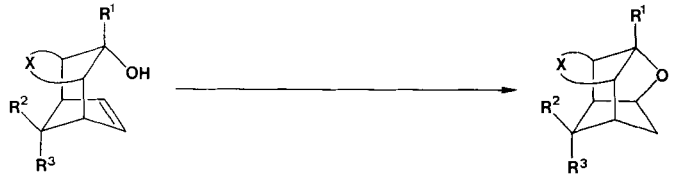
An electronic effect, in addition to the above mentioned proximity effect, plays an important role in compounds **1–4** containing a keto group ($R^2, R^3=O$). The rate of the base-catalyzed cyclization to the ethers **11–14** is much enhanced by way of homoconjugative stabilization (**b**$^1 \leftrightarrow$ **b**^{2}) of the intermediate carbanion *(Scheme 2)*. **11–14** are finally formed by homoketonization of the corresponding homoenolate **b** (= **b**$^1 \leftrightarrow$ **b**^{2})[4]).

In the case of compound **2** such a homoenolate **b** could be trapped with dimethyl sulfate: the homoenol methyl ether **21** was isolated in 56% yield. In addition, ether **22** (32%) was obtained, the product from direct methylation of the initial alkoxide ion *(Scheme 3)*.

We then turned our attention to the stereochemical course of the homoketonization under acidic (**21→12**) and in view of the base-catalyzed ether formation

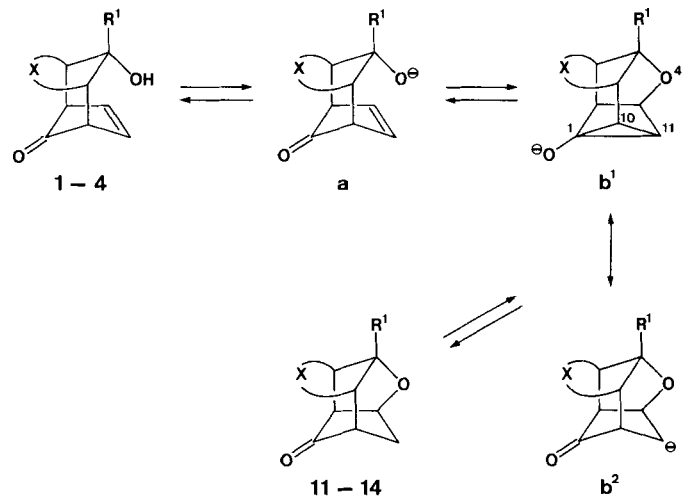
[4]) The phenomenon of homoenolization has attracted considerable interest in recent years. A first report appeared back in 1962 by *Nickon & Lambert* [3], many further examples were studied since. For representative reviews and some of the most recent communications see [4] and references cited therein.

Scheme 1



	R^1	R^2	R^3	X	
1	H	O		CH=CH	11
2	CH_3	O		CH=CH	12
3	H	O		CH_2–CH_2	13
4	CH_3	O		CH_2–CH_2	14
5	H	OCH_3	H	CH=CH	15
6	CH_3	OCH_3	H	CH=CH	16
7	H	H	H	CH_2–CH_2	17
8	CH_3	H	H	CH_2–CH_2	18
9	H	H	H	CH_2–CH_2–CH_2	19
10	CH_3	H	H	CH_2–CH_2–CH_2	20

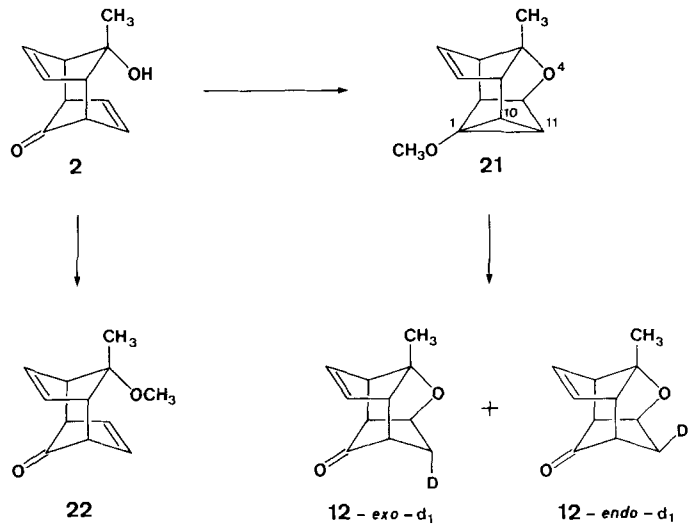
Scheme 2



especially under basic conditions (**b** → **11**–**14**). In each case there are *a priori* two possibilities for an electrophile to attack the three membered ring at the carbon atom C(11): either from below (the *exo*-side), which formally corresponds to retention of configuration or from above (the *endo*-side), which formally corresponds to inversion of configuration.

Thus the homoenol methyl ether **21** was treated with 0.15 N DCl in CH_3OD as well as with 1.3 N DCl in CH_3OD/D_2O 4:1 at room temperature. Attack by the

Scheme 3



Scheme 4

	R^1	R^2	R^3	
1	H	O		11 - *exo* - d_1
2	CH_3	O		12 - *exo* - d_1
6	CH_3	OCH_3	H	16 - *exo* - d_1

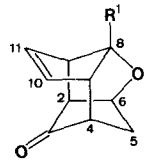
electrophile at the three membered ring occurred regioselectively at C(11), however without any stereoselectivity. An approximately 1:1 mixture of the two monodeuteriated ethers **12**-*exo*-d_1[5]) and **12**-*endo*-d_1[5]) was formed *(Scheme 3)*. This represents one of the very few cases, where homoketonization under acidic conditions occurs not predominantly (or even exclusively) under retention[6]). It has to be mentioned that the olefin alcohol **2** remained unchanged under the same reaction conditions. Therefore ether ring opening and subsequent recyclization can be ruled out as a possible pathway for the homoketonization of **21** to **12**.

In order to study the stereochemical course of the homoketonization under basic conditions we treated both **1** and **2** with base in deuteriated media at room

[5]) Deuterium incorporation (position, configuration and amount) was determined by ^{1}H-NMR.

[6]) Only a few examples are known, where ring opening occurs under inversion, see *e.g.* [4k] and [5].

Scheme 5



	R^1
11	H
12	CH_3

Table 2. *Deuterium incorporation in* **11** *and* **12** *by treatment with* t-*BuOK*/t-*BuOD*

Run	Starting material[a])	*t*-BuOK/ *t*-BuOD molality	Temp. °C	Time h	Yield	% Deuterium incorporation[5])				
						D–C(2)	*exo*-D–C(5)	*endo*-D–C(5)	D–C(10)	D–C(11)
1	**11**	0.9	100	15	95%	–	–	–	–	–
2	**11**	1.1	150	15	95%	90	30	–	80	80
3	**11**	1.0	150	24	quant.	95	45	–	85	85
4[9])	**11**	1.0	150	72	90%	85	75	10	85	85
5[9])	**11**	1.1	180	26	80%	95	80	20	85	85
6	**12**	1.0	25	24	quant.	–	–	–	–	–
7	**12**	1.0	120	24	quant.	–	–	–	15	15
8	**12**	1.0	150	24	95%	95	30	–	80	80
9	**12**	1.0	180	24	95%	90	65	–	85	85

[a]) 0.1 mmol/0.5 ml *t*-BuOK/*t*-BuOD.

temperature (2 N aq. (D_2O) NaOD/CH_3OD 1:1: **1** and **2**; 1 molal *t*-BuOK/*t*-BuOD: **1** and **2**; 1 N $NaOCH_3/CH_3OD$: **2**). In all experiments one deuterium atom was incorporated, regioselectively at C(5) and stereoselectively from the *exo*-side[5]) (retention) to yield **11**-*exo*-d_1 and **12**-*exo*-d_1, respectively *(Scheme 4)*. The configuration of the deuterium atom is the same as in **16**-*exo*-d_1, the product resulting from base treatment (2 N aq. (D_2O) NaOD/CH_3OD 1:1) of **6** by way of *trans*-antiplanar addition to the C,C double bond.

For further proof of the homoenolate **b** being an intermediate in the base-catalyzed ether formation from the olefin alcohols **1**–**4** to the corresponding ethers **11**–**14**, we also investigated the homoenolization of the ethers **11** and **12** *(Scheme 5)* by treatment with *t*-BuOK in *t*-BuOD. The results are listed in *Table 2*. The following conclusions can be deduced thereof:

a) analogous behaviour is observed whether the starting material is unmethylated at C(8) (**11**) or methylated (**12**);

b) at temperatures below 100° no deuterium is incorporated (runs 1 and 6);

c) at temperatures around 150° for 15–24 h (runs 2, 3, 8 and 9) deuterium incorporation at several positions[7]) is observed. Incorporation at C(5) results from the homoenolate **b** being an intermediate. The fact that on the one hand deuterium is incorporated neither at C(4) nor at C(6) and on the other hand at C(5) exclusively

[7]) Two main factors seem to be responsible for the ease of deuterium incorporation at the olefinic sites C(10) and C(11) (runs 2–5 and 7–9): on the one hand the enhanced acidity of a hydrogen atom at a sp^2- versus a sp^3-carbon atom, on the other hand an activating effect by the near keto group. For comparative studies, see [6].

from the *exo*-side proofs that both processes, homoenolization and homoketonization, proceed fully regio- as well as stereoselectively[8][9]);

d) deuterium incorporation at C(2), at only one of the two bridgehead carbon atoms C(2) and C(4) adjacent to the keto group (see runs 2–5, 8 and 9) implies that no symmetrical species is involved in the reaction sequence and by consequence a ring-open alkoxide ion **a** *(Scheme 2)* can clearly be ruled out as an intermediate.

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[8]) The same regio- and stereoselectivity results in the base treatment of **1** (→ **11**-*exo*-d_1) and **2** (→ **12**-*exo*-d_1) *(Scheme 4).*

[9]) The loss of stereoselectivity at C(5) observed in runs 4 and 5 is due to prolonged reaction time and/or higher temperature. Such an effect was already described on other systems by *Nickon et al.* [7].