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A Mechanistically Unusual Base Induced [1,3]-H-Shift in Homoallylic Ethers

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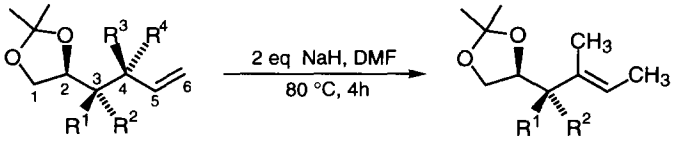
Abstract: Upon treatment with NaH in DMF the homoallylic ethers ***1a-g*** and the amine ***1h*** undergo a rearrangement into the trisubstituted (*E*)- olefins ***2a-h***. Experiments with isotopically labelled forms of ***1a*** and ***1b*** show that the [1,3]-shift is cleanly intramolecular and proceeds predominantly in the suprafacial mode. © 1997 Elsevier Science Ltd.

Base induced allylic migrations of terminal double bonds in hydrocarbons have been repeatedly investigated.[1] Particularly noteworthy are the pioneering studies by Cram and Uyeda on the mechanism of the rearrangement of non-racemic 3-phenyl-1-butene to (*E*)-2-phenyl-2-butene in alcoholic media such as KO*t*-Bu/*t*BuOH. Typically, the intramolecularity of this [1,3]-H-shift never exceeded 56 %.[2]

We found that the non-racemic O-protected homoallylic alcohols[3] **1a** - **1g** and amine **1h** undergo a similar yet *strictly intramolecular* [1,3]-H-shift[4] under *aprotic* basic conditions (DMF/NaH) to form the trisubstituted (*E*)-olefins **2a-h** exclusively. For **1a** - **1g** the yield strongly depends on the nature of the O-protective group: Bn gave by far the best results, all other protective groups were clearly inferior (Table 1).



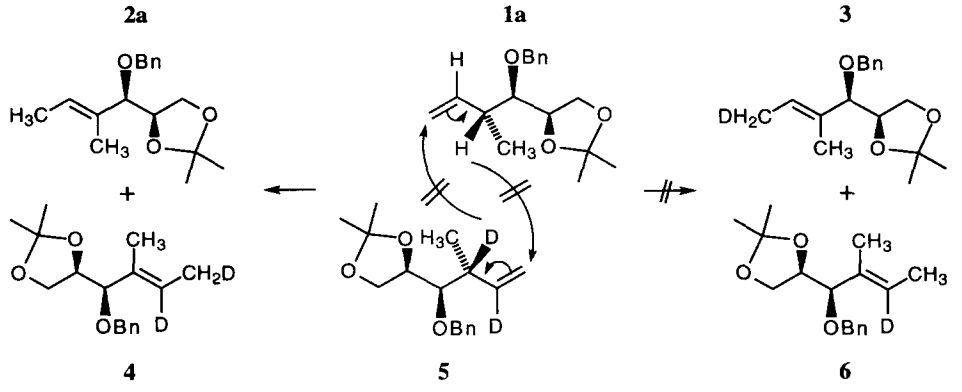
1 **2**

Table 1. Yields for the rearrangement of ethers **1a** - **1g** and amine **1h**.

Educt	R^1	R^2	R^3	R^4	Product	Yield (%)
1a	OBn	H	H	CH_3	**2a**	> 95
1b	H	OBn	CH_3	H	**2b**	> 95
1c	H	OBn	H	CH_3	**2c**	> 90
1d	O-CH_2-4-OMe-Ph	H	H	CH_3	**2d**	67
1e	O-CH_2-4-Cl-Ph	H	H	CH_3	**2e**	63
1f	O-THP	H	H	CH_3	**2f**	38
1g	O-CH_3	H	H	CH_3	**2g**	3
1h	H	NBn_2	H	CH_3	**2h**	35

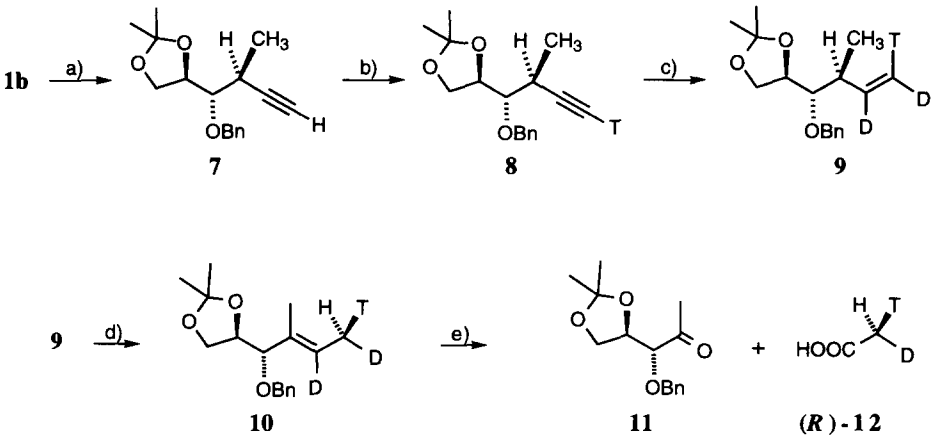
From the fact that the reaction proceeds equally well with the diastereomers **1a** (2*R*,3*R*,4*R*), **1b** (2*R*,3*S*, 4*S*) and **1c** (2*R*,3*S*,4*R*) it is concluded that the relative configurations of the crucial positions 3 and 4 have no influence on the rearrangement. Apparently, the reaction is limited to NaH as the base and DMF or

tetramethylurea (TMU) as solvents; attempts to rearrange **1a** in NaH/DMSO or KH/DMF resulted in incomplete turnovers. Other bases and solvents such as NaH in xylene, DBU, DABCO, LDA in THF, $NaN(CH_3)_2$ in DMF, KO*t*Bu in *t*BuOH or DMF or $NaOCH_3$ in CH_3OH left the substrate unchanged. As one mole of hydrogen was evolved from NaH and DMF or TMU, respectively, it appears that one of the N-CH_3 groups is deprotonated at 80 °C to form the reactive agent. However, all experiments to identify such a species have failed so far. Both **2a** and its (*Z*)-isomer (prepared on an independent route) remain unchanged under the conditions, which demonstrates that the reaction is irreversible and its (*E*)-selectivity is the result of kinetic control. The strictly intramolecular course of the [1,3]-H-shift was demonstrated by heating a 1:1-mixture from ether **1a** and its dideuteriated analogue **5** in NaH/DMF (Scheme 1). Only the undeuteriated (**2a**) and the dideuteriated (**4**) rearrangement products were found according to 500 MHz ^1H NMR analysis and HRMS. None of the monodeuteriated compounds **3** or **6** could be detected. Additionally, the rearrangement of **1a** into **2a** was studied kinetically and was found to be first order with respect to **1a**. In a second experiment the reaction was followed by ^1H NMR spectroscopy in d_7-DMF. Apart from small impurities (< 5 %) the signals of **1a** and **2a** only were detectable. These results indicate that after protonation the unknown base must act as a monohydric acid so that the accepted proton can be redelivered to the substrate.

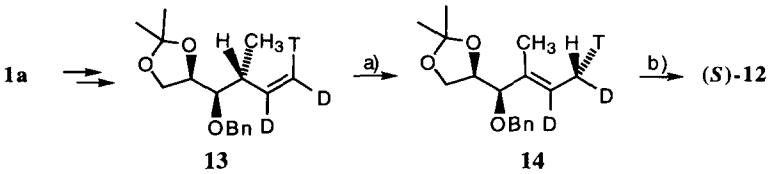


Scheme 1. Negative Crossover Experiment.

To investigate the stereochemical course of the rearrangement, the triply labelled compound **9** was synthesized from **1b** by the stereochemically unambiguous route shown in Scheme 2 and then submitted to the standard isomerization conditions. Ozonolysis of the resulting olefin **10** followed by oxidative workup with H_2O_2 yielded, in addition to ketone **11**, a specimen of chiral acetic acid (**12**) which was found by the usual enzymatic analysis[5] to possess predominantly the (*R*)-configuration with an ee of 38 %. In a similar set of reactions, compound **13**, a stereoisomer of **9**, was prepared from **1a** and then converted, via **14**, into a specimen of (*S*)-acetic acid (*S*)-**12** with an ee of 34 % (Scheme 3). These results demonstrate that the intramolecular [1,3]-H-shift in **1a** and **1b** proceeds with a 2:1 ratio of suprafacial *vs.* antarafacial migration.



Scheme 2. Reagents and Conditions : a) 1. O_3, PPh_3, CH_3OH, - 78 °C, 2. CBr_4, PPh_3, Zn, CH_2Cl_2, 3. nBuLi, hexane, - 78 °C, 4. H_2O, 66 %. b) 1. nBuLi, THF, 2. T_2O (100 mCi/mL); c) D_2 (1 bar), $Pd/BaSO_4$, CH_3OH, quinoline. d) 2 eq NaH, DMF, 80 °C, 15 h, 58 % (3 steps). e) O_3, H_2O_2, CH_2Cl_2, 87 %.



Scheme 3. Reagents and Conditions: a) 2 eq NaH, DMF, 80 °C, 15 h; b) oxidation, overall yield 31 %.

Our results differ considerably from those obtained by Cram/Uyeda in protic media.[2] These [1,3]-H-shifts proceeded with incorporation of deuterium from the solvent into the rearranged olefin and, to a much lesser degree into the starting material, and were largely intermolecular. Moreover, the reaction required activating substituents such as phenyl at the reaction site. Points of similarity between Cram's system and ours, however, can be seen in the irreversibility of the rearrangement and the high stereocontrol exerted on the newly created olefinic double bond . There are examples in the literature[6] for intramolecular base-catalyzed [1,3]-H-shifts, where the rate of the reprotonation of the carbanionic species is obviously much higher than that of the H/D-exchange with the reaction medium. However, as in Cram's case all these experiments were performed with clearly defined bases in protic media. In no case, the supra- or antarafaciality of the H-shift has been studied.

In conclusion, our rearrangement follows a mechanistic pathway which is clear as far as the substrate is concerned. The nature of the base and, hence, the details of the de- and reprotonation processes, however, remain to be clarified. Nevertheless, the rearrangement has proven its value in the total synthesis of various natural products, such as (+)-citreoviral[7], (-)-ACRL toxin III B[8] and α,β-unsaturated γ-amino acids.[9]

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Dedicated to Professor Peter Welzel on the occasion of his 60th birthday

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4. *Typical procedure for the [1,3]-shift.*: NaH (0.63 g, 26 mmol) in mineral oil suspension was washed with hexane, dried and added to **1a** (3.51 g, 12.7 mmol) in DMF (50 mL) and the mixture was stirred at 80°C for 4 h (TLC-control). Ice was added, DMF was removed under reduced pressure and the residue was diluted with water (30 mL) and extracted with dichloromethane (3 x 30 ml). The organic layers were combined, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (silicagel, ethyl acetate/hexane) furnished **2a** (3.34 g, 95 %) as a colorless oil. $[\alpha]^{20}_D$ = -51.9 (c = 2.1, chloroform). ^{1}H NMR (270 MHz, $CDCl_3$, TMS): δ = 1.38 (s, 3 H), 1.40 (s, 3 H), 1.59 (s, 3 H), 1.64 (d, J = 5 Hz, 3 H), 3.55 (t, J = 8 Hz, 1 H), 3.65 (d, J = 7 Hz, 1 H), 3.84 (t, J = 8 Hz, 1 H), 4.26 (m, 1 H), 4.35 and 4.57 (d, J = 12 Hz, 2 H), 5.51 (quart, J = 5 Hz, 1 H), 7.82 (m, 5 H). ^{13}C NMR (62.5 MHz, $CDCl_3$, TMS): δ = 10.9, 13.27, 25.3, 26.7, 67.5, 69,5, 75.6, 85.9, 109.1, 125.8, 127.4, 127.7, 128.2, 132.4, 138.3. MS (EI) : m/z = 276 (M+), 261, 175, 101, 91.
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