Enantiospecific Brook Rearrangement of Tertiary Benzylic α-Hydroxysilanes


DOI
10.1002/ejoc.201701469

Publication date
2018

Document Version
Final published version

Published in
European Journal of Organic Chemistry

License
Article 25fa Dutch Copyright Act (https://www.openaccess.nl/en/in-the-netherlands/you-share-we-take-care)

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (https://dare.uva.nl)

Download date: 27 Sep 2023
Enantiospecific Brook Rearrangement of Tertiary Benzylic \( \alpha \)-Hydroxysilanes

Juan F. Collados, Pablo Ortiz, Juana M. Pérez, Yiyin Xia, Mark A. J. Koenis, Wybren J. Buma, Valentin P. Nicu, and Syuzanna R. Harutyunyan*

Abstract: The Brook rearrangement of simple, chiral tertiary benzylic \( \alpha \)-hydroxysilanes is presented. The rearrangement followed by proton trapping is enantiospecific and proceeds with inversion of the configuration at the carbon center. Importantly, the [1,2]-Brook rearrangement can be followed by trapping of methyl or allyl electrophiles even in the protic environment, although with minimal retention of chirality.

Introduction

Since its discovery, the [1,2]-Brook rearrangement, defined as the reversible transformation from \( \alpha \)-silyl oxyanions to \( \alpha \)-silyl-\( \alpha \)-silyl-oxy carbanions (Scheme 1), has attracted considerable attention, both regarding the mechanism and its implementation in organic synthesis. Recently, Marek et al. and our group independently reported the stereoselective [1,2]-Brook rearrangement-trapping sequence of allylic hydroxysilanes. The presence of either an allyl or alkenyl group in the hydroxysilane is a common feature in enantiospecific variants of the [1,2]-Brook rearrangement because of the enhanced configurational stability of the carbanion after migration of the metal to the beta carbon. Another interesting reaction sequence involving stereoselective Brook rearrangement/acylation sequence was reported by Johnson et al. Conversely, \( \alpha \)-hydroxysilanes lacking configuration stabilizing groups have been less explored in the [1,2]-Brook rearrangement.

Scheme 1. General [1,2]-Brook rearrangement.

Following the initial discovery of the Brook rearrangement both Brook and co-workers and Mosher and co-workers reported examples of the rearrangement of secondary benzylic \( \alpha \)-hydroxysilanes including the stereochemistry of the process. Brook et al. used a chiral silicon whereas Mosher et al. used chiral deuterated \( \alpha \)-hydroxysilanes, but both reported that the rearrangement proceeded with inversion of configuration at the carbon center (Scheme 2a). Shortly after, West et al. showed that the reverse rearrangement, the migration of silicon from oxygen to carbon, is also stereospecific and proceeds with inversion of configuration. Stereospecific Brook rearrangement was also reported for tertiary \( \alpha \)-hydroxysilanes with aliphatic six member cyclic structures. In these examples the stereospecificity of the rearrangement was rationalized by kinetic equatorial protonation of the anionic intermediate owing to the cyclic structure of the corresponding \( \alpha \)-hydroxysilanes.

Scheme 2. a) [1,2]-Brook rearrangement of deuterated secondary benzylic \( \alpha \)-hydroxysilanes reported by Mosher. b) Enantiospecific [1,2]-Brook rearrangement of tertiary benzylic \( \alpha \)-hydroxysilanes.

Recently we developed catalytic asymmetric addition of Grignard reagents to acylsilanes, which for the first time allows access to enantioenriched chiral tertiary benzylic \( \alpha \)-hydroxysilanes. Here we report our findings on Brook rearrangements of these tertiary benzylic \( \alpha \)-hydroxysilanes and the stereochemistry of the process (Scheme 2b).
Results and Discussion

We started investigating the reaction of benzyl α-hydroxysilane 1a\(^{[9]}\) (90 % ee) with a variety of metal bases that could trigger the Brook rearrangement. A mixture of 1a and the corresponding base (1 equiv.) was stirred overnight in THF at room temperature and then quenched and analyzed by \(^1\)H NMR spectroscopy. Et\(_2\)Zn, which initiated the Brook rearrangement for allylic hydroxysilanes\(^{[3]}\) did not work for the benzyl counterpart and deprotonation with MeMgBr did not trigger the rearrangement either. In both cases, forcing of the reaction conditions by a light warm up resulted in decomposition products. In contrast, deprotonation with MeMgBr did not trigger the rearrangement with full conversion. Alcohol did take place and the corresponding product was then cleanly obtained after desilylation with TBAF (Table 1, entry 1) with an ee of 40 %. Subsequently we studied the influence of the different reaction parameters on the stereoselectivity of the process (Table 1). The first experiment had been carried out with one equivalent of LiOtBu. However, since it is known that even catalytic amounts of a base can trigger the Brook rearrangement,\(^{[1,2a]}\) we tried to reduce the amount of LiOtBu. With 0.5 equivalents of base the outcome was the same as with 1 equiv. but, interestingly, from that point on, decreasing the amount of base resulted in an increase of the ee of the product. With 20 % of LiOtBu the enantioselectivity rose to 75 % and with 5 % of base the product was obtained with nearly full transfer of chirality (entries 2–4). Only with 1 % of LiOtBu no Brook rearrangement took place (entry 5).

Table 1. Conditions screening for the enantiospecific Brook rearrangement.\(^{[a]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal base (equiv.)</th>
<th>Temp. [°C]</th>
<th>Conv. [%][b]</th>
<th>ee [%][c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiOtBu (100 %)</td>
<td>r.t.</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>LiOtBu (50 %)</td>
<td>r.t.</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>LiOtBu (20 %)</td>
<td>r.t.</td>
<td>100</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>LiOtBu (5 %)</td>
<td>r.t.</td>
<td>100</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>LiOtBu (1 %)</td>
<td>r.t.</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>LiOtBu (5 %)</td>
<td>–78 to r.t.</td>
<td>100</td>
<td>88</td>
</tr>
<tr>
<td>7</td>
<td>LiOtBu (5 %)</td>
<td>–50</td>
<td>100</td>
<td>73</td>
</tr>
<tr>
<td>8</td>
<td>LiOtBu (5 %)</td>
<td>0</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>MeMgBr (5 %)</td>
<td>r.t.</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>Et(_2)Zn (5 %)</td>
<td>r.t.</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>Me(_3)Al (5 %)</td>
<td>r.t.</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>12</td>
<td>KOtBu (5 %)</td>
<td>r.t.</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>13</td>
<td>Li napthoxide (5 %)</td>
<td>r.t.</td>
<td>80</td>
<td>84</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 0.1 mmol of 1a, 1 mL of THF and base. Stirred for 3–24 h. Deprotected using TBAF (tetrabutyl ammonium fluoride). [b] Determined by \(^1\)H NMR spectroscopy. [c] Enantiomeric excess was determined by chiral HPLC.

This behavior can be rationalized on the basis of different equilibria controlling the reactions under catalytic or stoichiometric conditions. It is known that with catalytic amounts of base the equilibrium depends on the relative stabilities of the neutral hydroxysilane and silyl ether, while with excess of base the equilibrium is determined by the relative stabilities of the charged species, namely the alkoxide and the carbanion (Scheme 1).\(^{[2a]}\)

We then studied the effect of the temperature on the reaction. No reaction took place at –78 °C, but adding the base at –78 °C and letting it slowly warm up to room temperature yielded the product in 88 % ee (entry 6). The Brook rearrangement was also observed at –50 °C, yielding the product in slightly lower ee (73 %), and at 0 °C, giving results that approach those at room temperature (entry 8). These results clearly indicate that there is no particular dependence of the enantioselectivity of the process on the temperature, but that, as expected, longer reaction times are required to reach full conversion at low temperature (3 h at room temp. vs. overnight at –50 °C). Finally we examined the role of the metal base under catalytic conditions (entries 9–13). In line with the initial experiments described above, no Brook rearrangement took place using MeMgBr or Et\(_2\)Zn as a base, while Me\(_3\)Al also did not trigger the rearrangement. Interestingly, with KOtBu full conversion to 2a was observed and lithium napthoxide triggered the Brook rearrangement too. From these results it can be concluded that only alkali metals trigger the Brook rearrangement. This is further supported by the observation that NaH can start the process as well (not shown in the Table). Alkoxides formed from alkali metals are expected to be less stable than those derived from Mg, Zn or Al, which could be the reason for the rearrangement taking place.

With the aim of studying the electronic effects in the carbon and the influence of the silicon center in the stereoselectivity of the rearrangement we conducted further experiments. First we synthesized several structural analogues of the standard hydroxysilane 1a and subjected them to the Brook rearrangement (Table 2). Products 2b–e were obtained after overnight reactions. The enantioselectivities of the deprotected products 3b–e were slightly lower than the original values for the starting silylated alcohols 1b–e. Both substrates 1b and 1c, with electron withdrawing and donating groups, respectively, had the same loss of 12 percentage points of ee (entries 2–3). This

Table 2. Influence of the substrate substituents on the Brook rearrangement.\(^{[a]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate, ee [%]</th>
<th>R</th>
<th>Si moiety Product, ee [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a, 90</td>
<td>H</td>
<td>SiPh(_2)Me</td>
</tr>
<tr>
<td>2</td>
<td>1b, 85</td>
<td>F</td>
<td>SiPh(_2)Me</td>
</tr>
<tr>
<td>3</td>
<td>1c, 92</td>
<td>rBu</td>
<td>SiPh(_2)Me</td>
</tr>
<tr>
<td>4</td>
<td>1c, 92</td>
<td>rBu</td>
<td>SiPh(_2)Me</td>
</tr>
<tr>
<td>5</td>
<td>1d, 24</td>
<td>OMe</td>
<td>SiPh(_2)Me</td>
</tr>
<tr>
<td>6</td>
<td>1e, 75</td>
<td>H</td>
<td>SiPhMe(_2)</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 0.1 mmol of 1, 1 mL of THF, 5 mol-% of LiOtBu. Stirred for 3 h to 24 h depending on the substrate. The intermediate silyl ether was deprotected using TBAF (tetrabutyl ammonium fluoride). [b] Enantiomeric excess was determined by chiral HPLC. [c] The reaction was stopped and analyzed after 20 % conversion. [d] 80 % yield in Brook rearrangement after overnight reaction.
indicates that electronics play a minimal role in the transfer of chirality during the rearrangement step. This is corroborated by entry 5, where methoxy, a very strong electron donating group, was used and the same enantioselectivity was obtained after the rearrangement.

Similarly, the substitution at the silicon atom does not seem to affect the stereoselective outcome of the Brook rearrangement either, as the loss of chirality with compound 1e corresponds to 15 % ee, comparable to the other results (entry 6). To investigate if the ee changes as the reaction progresses, an experiment using substrate 1c was carried out, quenching the reaction after 5 h, with a 20 % of conversion to the product 2c. An increased enantioselectivity of 85 % observed in this case (compared to 81 % ee at full conversion, entry 3) might be related to the amount of base with respect to substrate. At conversions higher than 75 % the amount of base with respect to the remaining substrate resembles the same situation as in entries 1–4 in Table 1, where the increased amount of base causes a decrease in enantioselectivity. Therefore it is likely that the last 20 % of the substrate is converted into the product with lower enantioselectivity, thus leading to an overall decrease in enantioselectivity at full conversion.

Original [1,2] Brook rearrangement of secondary benzylic α-hydroxysilanes has been reported to proceed with inversion of configuration.\(^{[6,10]}\) In order to see if this holds true for the tertiary counterparts we determined the absolute configuration of the starting material 1a and that of the product 3a. The latter was determined to be S by comparison with the reported optical rotation.\(^{[10]}\) Vibrational Circular Dichroism (VCD) was used for determining the absolute configuration of the starting material 1a (for further details see Supporting Information).\(^{[11]}\) We measured the VCD spectra of both hydroxysilane 1a and ent-1a (Figure 1) and found that the first fitted well with the calculated spectra for the S enantiomer (Figure 2). We thus conclude that the Brook rearrangement of tertiary benzylic α-hydroxysilanes proceeds with inversion of configuration.

We tested several electrophiles, including acyl chlorides, aldehydes, alkyl halides and Michael acceptors, but only methyl iodide and allyl bromide led to the corresponding trapping products 4, which were racemic (Scheme 3). Variable amounts of protonated product 3a were also obtained in these reactions, due to the competition with protonation. When the presence of protons in the media was avoided by using nBuLi, full conversion to the trapping products 4a–b was achieved, but the product was again racemic. This can be rationalized on the basis that carboniums without any stabilizing substituents will racemize very fast. Consequently, we thought of configurationally stabilizing the carbanion using an external Lewis base that can coordinate both with silicon and lithium atoms. DMF, HMPA and TMEDA were tried for this purpose but unfortunately the ee did not surpass 8 % (Scheme 3).

Original [1,2] Brook rearrangement do not propose a mechanism to explain the stereochemical outcome. For secondary benzylic α-hydroxysilanes we distinguish three possible scenarios:\(^{[6,10]}\) 1) fast protonation of the carbanion before flipping takes place; 2) transfer of the proton from the solvated base to the carbon in the pentacoordinate intermediate; 3) transfer of the proton from the base coordinated to the oxygen to the carbon in the pentacoordinate intermediate.

Our results seem to suggest the third scenario. We therefore propose a mechanism in which LiO\(_{tBu}\) deprotonates the hydroxysilane 1a, followed by the attack of oxygen to the silicon and formation of the pentacoordinate intermediate. We believe that at this stage the proton is trapped directly from the pentacoordinate silicon intermediate, as it is in the vicinity thanks to the coordination of the nBuOH to the lithium (Scheme 4). Support for the intramolecular mechanism was gained when the deprotonation/Brook rearrangement was carried out with nBuLi and the reaction was warmed up before adding the proton source. In this case the corresponding protonated product was formed, but completely racemic. The proposed concerted

![Figure 1. Measured VCD spectra of compounds 1a and ent-1a.](image)

![Figure 2. Experimental and calculated IR and VCD spectra of compound 1a.](image)

![Scheme 3. Brook rearrangement/trapping of carbon electrophiles tandem attempts.](image)
mechanism would explain the enantiospecificity of the reaction in the case of trapping of protons and the loss of it for external electrophiles. In the latter case the pentacoordinate silicon intermediate would evolve to the chiral carbanion which would quickly racemize and thus the product of the trapping would lose the enantioenrichment (Scheme 4).[6b]

Scheme 4. Proposed mechanism for the stereospecific protonation of tertiary benzylic α-hydroxysilane 1a.

Conclusions

In summary, we have explored the Brook rearrangement of simple, chiral tertiary benzylic α-hydroxysilanes. We have demonstrated that the rearrangement followed by proton trapping is enantiospecific and proceeds with inversion of the configuration at the carbon center analogously to their secondary counterparts. Moreover, we have found that a catalytic amount of base is not only sufficient, but beneficial for the enantiospecificity of the process. Importantly, the [1,2]-Brook rearrangement can be followed by trapping of methyl or allyl electrophiles even in a protic environment, however, in all cases with minimal retention of chirality.

Acknowledgments

Financial support from The Netherlands Organization for Scientific Research (NWO-Vidi and ECHO to S. R. H.) and the Ministry of Education, Culture and Science (Gravity program 024.001.035 to S. R. H.) is acknowledged. J. M. P. thanks to the European Commission for an Intra-European Marie Curie fellowship (grant 746011 --ChirPyr). This research received further support from NWO in the framework of the Fund New Chemical Innovations (NWO Project Nr. 731.014.209).

Keywords: Synthetic methods · Rearrangement · Hydroxysilanes · Enantiospecific · Chirality