THE USE OF RIEKE ZINC METAL IN THE SELECTIVE REDUCTION OF ALKYNES

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Summary: Ricke zinc has been found to be a very selective reducing agent of alkynes to *cis*-alkenes, allowing for the reduction of enynes to 1,3-dienes, diynes to enynes or dienes, and of propargylic alcohols to *cis*-allylic alcohols.

In our recent synthesis of 4,5-dihydrooxcpins from enynols,¹ it was necessary to selectively reduce the alkyne to the corresponding *cis*-alkene (eq. 1). Traditional methods for doing this reduction, such as catalytic hydrogenation with Lindlar's catalyst or diimide reduction worked poorly with the unprotected alcohol,² leading to mixtures of products from which the *cis*-dienol could be isolated only after tedious chromatography. We found that Rieke zinc metal³⁻⁶ was a superior reagent for effecting this reduction, leading to both high cis selectivity and excellent yields without any over reduction of the desired dienol product. We report herein our further investigations of these reaction conditions for the selective reduction of alkynes (see Table I).

$$R^{2} \xrightarrow{\text{OH}} H^{2} \xrightarrow{\text{Rieke Zn}} H^{1} \xrightarrow{\text{Rie$$

Among the examples included in the table are those from our previous work (entries a-e)¹ involving 5-en-3-yn-2-ols. Among these five examples, all of which are 2° enynols, only the isopropenyl derivative **1b** gave any appreciable amount (~5%) of the undesired product from trans reduction of the alkyne. In seeking to improve the selectivity of the zinc reduction of this alcohol, it was found that protection of the alcohol as its *t*-BuMe₂Si- ether (1.5 equiv *t*-BuMe₂SiCl, 1.5 equiv imidazole, DMF, RT, 30 min, 84%) led to a slower but more selective cis reduction of the alkyne (entry i). This reduction of conjugated enynes in which the alkyne is part of a propargylic alcohol has also been extended to 1° and 3° alcohols. Rieke zinc reduction of 1° enynol **1f** was straightforward, giving **2f** from cis reduction of the alkyne. A more challenging test of this methodology was the reduction of 3° enynols **1g** and **1h**, since non-bonded interactions in the *cis*-alkene product would be maximum among the enynols examined. In the event, 3° alcohol **1g** was reduced with the same high selectivity for the *cis*-alkene as observed for the 1° and 2° enynols. However, reduction of enynol **1h**, whose analogous 2° alcohol **1b** gave the lowest selectivity among those examined, led to lessened selectivity for the cis isomer over the trans (3:1).

One notable feature of the reductions of enynes 1a-f was their completion within 10-60 minutes at 65 °C, whereas most other examples⁵ of zinc reductions of conjugated enynes required more vigorous conditions. Although this can be explained in part by the greater reactivity of Rieke zinc versus other methods of activating zinc, it seemed plausible that the proximity of the alcohol moiety to the alkyne might be playing a significant role in these reductions.⁷ One way to test this hypothesis was to switch the positions of the alkene and the alkyne in the enynols relative to the position of the alcohol. To this end, *trans*- and *cis*-3-en-5-yn-2-ols 3 and 5 (entries j and k) were prepared and subjected to Rieke zinc reduction. For both 3 and 5, the yield and selectivity for cis reduction of the alkyne were similar to the results previously observed for comparable 5-en-3-yn-2-ols (entries d and e), but the progress of the reaction was noticeably slower. The increased reactivity of an alkyne that is part of a propargylic alcohol was further demonstrated by the selective reduction of 3,5-diyn-2-ol 6 (entry 1). By



Table I. Rieke Zinc Reductions of Conjugated and Non-Conjugated Progargylic Alcohols⁸

^aSee reference 4 for further details on the experimental procedure and references 11 and 13 for the preparation of starting materials and ¹³C NMR data. ^bRatios were determined from ¹H and ¹³C NMR spectra. ^cYields were of isolated material following work-up without further purification unless otherwise noted. ^dYield following flash chromatography on SiO₂. ^eYield following distillation. ^fThe reaction was allowed to stand for 11 hours following reflux for 2.5 hours. ^g**2f-g** were very acid sensitive and prone to dehydration.

controlling both the stoichiometry and the time period of the reaction (2 equiv Rieke zinc, 10 min), the major product was that from cis reduction of the 3-alkyne to give 3-en-5-yn-2-ol 5. Small amounts of the products from cis reduction of the 5-alkyne (1e), cis reduction of both alkynes (2e), and trans reduction of the 3-alkyne (3) were

also observed. By using a larger excess of Rieke zinc and a longer reaction time (6 equiv Rieke zinc, 19 h, entry m), it was possible to reduce both alkynes, leading in high yield to the *cis,cis*-3,5-dien-2-ol **2e** as the major product.

Given that almost all examples of reductions of alkynes with some form of zinc metal have been on alkynes conjugated with one or more alkene, alkyne or aryl group,⁸ it was of interest to see if the activation of an adjacent alcohol alone was sufficient to allow for the reduction of a nonconjugated alkyne. In fact, although less reactive than their conjugated counterparts, propargylic alcohols did undergo selective cis reduction with Ricke zinc in good yield. For example, reduction of 4-heptyn-3-ol (7) led to *cis*-4-hepten-3-ol (8) (entry n). Indeed, the activation of an alkyne within a propargylic alcohol was sufficient to allow for the selective reduction of that alkyne in the presence of another nonconjugated alkyne, as illustrated by the generation of enyne 10 from digne $9.^9$. The cis selectivity of these reactions nicely compliments the trans reduction of propargylic alcohols with NaAlH2(OCH2CH2OCH3)2.¹⁰

The Rieke zinc reduction of conjugated enynols and diynols makes readily available a variety of (E, Z)and (Z, Z)-1,3-dienes in excellent yield without the problem of over reduction. The reductions of 3-en-5-yn-2-ols and 5-en-3-yn-2-ols both proceed with high cis stereoselectivity and in excellent yield, but the latter compounds are more rapidly reduced. The activating ability of an adjacent alcohol on alkyne reduction shows promise as a method for chemoselective cis reduction of both conjugated and nonconjugated diynols, and of the cis reduction of simple propargylic alcohols. Further work on the use of these reaction conditions to selectively reduce alkynes is in progress and will be reported in due course.

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References

- (1) Clark, D. L.; Chou, W.-N.; White, J. B. J. Org. Chem. 1990, 55, 3975-7.
- (2) Catalytic hydrogenation with Lindlar's catalyst on enynols protected as the Me₃Si- or *t*-BuMe₂Si- ethers in hexanes led to improved selectivity for the cis reduction of the alkyne, but still led to gross mixtures.
- (3) Rieke, R. D.; Uhm, S. J. Synthesis 1975, 452-3.
- (4) The alcohol was added as a solution in MeOH to a refluxing suspension of Rieke zinc in THF, followed by the addition of a small amount of water (ratio of THF/MeOH/H₂O 7:5:1). Upon cooling, the reaction was filtered through Celite, diluted in ether, washed with 10% NH₄Cl, 10% NaHCO₃ and sat. NaC1, and dried with MgSO₄. For the number of equivalents of zinc, the length of time, and any purification, see Table I. More than a stoichiometric amount of zinc was used to ensure complete reduction of the alkyne, as the starting material and product often had similar chromatographic properties, and a small amount of starting material was difficult to detect by TLC. These conditions, which are similar to those used to reduce an enynol containing a homopropargylic alcohol,^{5e} have been used on scales ranging from 0.5-10 mmol (50 mg-2 g). In preparing Rieke zinc, a slight excess of ZnBr₂ to K was used to ensure that there was no K metal present when the MeOH and H₂O were added to the reaction. The use of zinc dust activated by washing with acid,^{5a} zinc dust/KCN,^{5b-c} Zn(Cu)^{5d,8b} (prepared by the method of Blankenship, Burdett and Swenton, J. Org. Chem. 1974, 39, 2300-1), or Zn(Hg) (prepared by the

method of Elphimoff-Felkin and Sarda, Org. Syn. 1988, Coll. Vol. VI, 769-73) in protic solvent systems gave inferior results.

- (5) Examples of the reduction of an enyne to a 1,3-diene using zinc metal in protic solvent systems include: (a) Morris, S. G.; Herb, S. F.; Magidman, P.; Luddy, F. E. J. Am. Oil Chem. Soc. 1972, 49, 92-4. (b) Näf, F.; Decorzant, R.; Thommen, W.; Willhalm, B.; Ohloff, G. Helv. Chim Acta 1975, 58, 1016-37. (c) Oppolzer, W.; Fehr, J.; Warneke, J. Helv. Chim. Acta 1977, 60, 48-58. (d) Aerssens, M. H. P. J.; Brandsma, L. J. Chem. Soc., Chem. Commun. 1984, 735-6. (e) Winter, M.; Näf, F.; Furrer, A.; Pickenhagen, W.; Giersch, W.; Meister, A.; Willhalm, B.; Thommen, W.; Ohloff, G. Helv. Chim. Acta 1979, 62, 135-9.
- (6) The use of Zn(Cu/Ag) has recently been used for the selective cis reduction of the alkyne in conjugated dienynes and trienynes. See: (a) Boland, W.; Schroer, N.; Sieler, C.; Feigel, M. Helv. Chim. Acta 1987, 70, 1025-40. (b) Avignon-Tropis, M.; Pougny, J. R. Tetrahedron Lett. 1989, 30, 4951-2.
- (7) It may be that the proximity of the alcohol aids the reaction by lowering the reduction potential of the alkyne through an inductive affect. Alternatively, the alcohol may accelerate the reaction by aiding in the adsorption of the alkyne onto the surface of the zinc metal^{5d} or through intramolecular proton transfer within an organozinc intermediate.
- (8) (a) For an example of the reduction of a terminal nonconjugated alkyne using copper plated zinc powder, see: Veliev, M. G.; Guseinov, M. M.; Mamedov, S. A. Synthesis 1981, 400. (b) For examples of the reduction of nonconjugated propargylic alcohols using Zn(Cu), see reference 5d and: Sondengaru, B. L.; Charles, G.; Akam, T. M. Tetrahedron Lett. 1980, 21, 1069-70.
- (9) The presence of one alkene and one alkyne in product 10 was clear from its ¹³C NMR spectrum. It was determined that it was the alkyne of the propargylic alcohol that had undergone reduction from the coupling of an olefinic hydrogen with the methinyl hydrogen of the carbinol carbon in the ¹H NMR spectrum. The olefinic geometry of the allylic alcohol was proved to be cis by preparing the alternative trans isomer by reduction of the diynol with NaAlH₂(OCH₂CH₂OCH₃)₂¹⁰ to give the *trans*-allylic alcohol (J_{olefinic}=15.6 Hz). The *cis*-enone from oxidation of the allylic alcohol from Rieke zinc reduction isomerized upon standing in CDCl₃ to the *trans*-enone from oxidation of the *trans*-allylic alcohol.
- (10) Denmark, S. E.; Jones, T. K. J. Org. Chem. 1982, 47, 4595-7.
- (11) For this study, many of the substrates were prepared by the Sonogashira coupling¹² of a terminal alkyne with a *cis* or *trans*-bromoalkene. See reference 1 and its supplementary data for experimental details. By this method the following starting materials in the table were made: 1f, coupling of *trans*-2-bromovinyltrimethylsilane with propargyl alcohol; 3 and 5, coupling of 1-heptyne with *trans* and *cis*-4-bromo-3-buten-2-ol, respectively; diynol 6, coupling of 1-heptyne with 4-iodo-3-butyn-2-ol. Diynol 9 was made by the addition of the lithium acetylide anion of 1,5-decadiyne (Farchan Laboratories) to acetaldehyde. Enynol 1g was prepared by the addition of the lithium acetylide anion of 1-ethynylcyclohexene to acetone. The reactants for entries h and n were purchased from Farchan Laboratories.
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- ¹³C NMR (55.3 Hz, CDCl₃) data reported relative to the center line of CDCl₃ as 877.0. If: 8 146.2.
 122.6, 87.6, 85.1, 51.4, -1.75. 2f: δ 138.0, 136.9, 133.3, 129.8, 58.7, -1.40. 1g: δ 134.8, 120.1, 91.1, 83.8, 65.5, 31.6, 29.2, 25.6, 22.3, 21.4. 2g: δ 137.6, 137.3, 129.0, 125.3, 72.4, 31.5, 29.2, 25.1, 22.5, 21.8. 2h: δ 145.2, 136.7, 129.2, 113.4, 75.0, 36.3, 29.3, 23.9, 8.4. 3: δ 145.0, 109.3, 91.3, 78.3, 68.3, 31.1, 28.4, 23.0, 22.2, 19.3, 13.9. 4: δ 136.8, 133.0, 127.7, 125.0, 68.7, 31.5, 29.3, 27.7, 23.4, 22.5, 13.9. 5: δ 144.9, 109.5, 96.4, 76.2, 66.2, 31.0, 28.3, 22.4, 22.1, 19.4, 13.9.
 6: δ 81.9, 77.1, 69.2, 64.3, 58.7, 31.0, 27.8, 24.1, 22.1, 19.2, 13.8. cis-4-hepten-3-ol (8): δ 133.9, 131.8, 69.0, 30.4, 21.0, 14.3, 9.6. 9: δ 83.1, 83.0, 81.4, 78.3, 58.4, 31.0, 24.5, 21.8, 19.3, 19.0, 18.3, 13.5.

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