Title
Palladium hydride promoted stereoselective isomerization of unactivated di(exo)methylenes to endocyclic dienes.

Permalink
https://escholarship.org/uc/item/8vt2b83f

Journal
Organic letters, 16(9)

ISSN
1523-7060

Authors
Jung, Michael E
Lee, Gloria S
Pham, Hung V
et al.

Publication Date
2014-05-01

DOI
10.1021/ol500710v

Peer reviewed
Palladium Hydride Promoted Stereoselective Isomerization of Unactivated Di(exo)methylenes to Endocyclic Dienes

Michael E. Jung,* Gloria S. Lee, Hung V. Pham, and K. N. Houk*

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States

Supporting Information

ABSTRACT: The exomethylenes of 2,6-disubstituted bicyclo[3.3.1]nonan-9-ones 2 are readily isomerized over a palladium catalyst under an atmosphere of hydrogen to predominantly form the isomer 3 with C₂ symmetry with very little formation of the analogous product with C₅ symmetry. A hydrogen source is essential to effect the rearrangement.

The isomerization of alkenes using catalytic amounts of transition metals and their complexes has been widely studied.¹ For example, allyl units bearing heteroatoms, e.g., allylic amines, alcohols, and ethers, can be easily converted to their propenyl isomers.² Allyl arenes can likewise be transformed into the alkylstyrene isomers.³ One can also effect an equilibration between E and Z alkene isomers.⁴ However, there has been little research on the isomerization of unfunctionalized alkenes. Of the few accounts reported, many use large transition-metal complexes, numerous additives, high temperatures, and long reaction times.⁵ For the synthesis of rugulosone, 1 (Figure 1),⁶ we required a simple protocol to prepare the bicyclo[3.3.1]nonadiene core and investigated the isomerization of a symmetric di(exo)methylene to the endocyclic diene. We tested this process on the simple analogue, 1,5-dimethyl-3,7-dimethylenebicyclo[3.3.1]nonan-9-one 2a. The required dienone 2a was prepared in one step by the tetraalkylation of 3-pentanone with 1-chloro-2-(chloromethyl)-2-propene. We report here the successful isomerization of this diene 2a to the desired C₂-symmetric bicyclo[3.3.1]nonadiene 3a and the isomerization of related analogues.

The double rearrangement of this substrate 2a to the C₂ isomer 3a rather than the C₅ isomer 4a (Scheme 1) would be required to give the natural product. We believed that 3a would be more stable than 4a due to the steric nonbonded interaction of the indicated hydrogens in 4a (Figure 2). Initial attempts to directly isomerize diene 2a with transition-metal catalysts such as Wilkinson’s or Crabtree’s catalyst failed to yield either 3a or 4a; only starting material was recovered (Scheme 2). The uniquely strained and/or hindered structure of the bicyclono-

Figure 1. Structure of rugulosone.

Figure 2. Structures of the C₂ and C₅ dienes.

Scheme 1. Isomerization of 2a To Give 3a and/or 4a

Scheme 2. Attempts To Isomerize 2a

Received: March 6, 2014
Published: April 11, 2014

2382 dx.doi.org/10.1021/ol500710v | Org. Lett. 2014, 16, 2382−2385
nane core may cause this lack of reactivity. Unable to directly isomerize the olefins, we examined a longer, more complicated process. Epoxidation of 2a (DMDO, 23 °C, 3 h) afforded the diepoxide 5 in 89% yield. All attempts at acid- or base-promoted ring-opening of these epoxides to give allylic alcohols failed, as did attempts to prepare the tertiary alcohols through various hydride reductions.

The desired isomerization was, however, effected by the use of an activated palladium catalyst mixed with hydrogen gas. Thus, treatment of 2a in methanol with 4 mol % of Pd/C under a balloon of hydrogen afforded the desired C2 isomer 3a along with the monoreduced isomerized product 6a and the fully reduced material 7a in a 68:28:4 ratio (by GCMS) (Scheme 3).

Scheme 3. Isomerization of 2a To Give 3a

A number of control experiments were conducted to demonstrate that hydrogen was required for this isomerization. The use of an argon atmosphere instead of hydrogen was unsuccessful. The use of ammonium formate (transfer hydrogenation) also produced the expected isomerization. Thus, it seems that the reaction requires a small amount of hydrogen to initiate the isomerization.

We postulated that alkene isomerization might be favored over reduction if the hydrogenation pathway could be slowed down, perhaps by a change in the solvent, since solvent effects on hydrogenation rates have been well studied. For that reason, various solvent systems were examined to see if solvent effects could improve the yield of isomerization (Table 1). Polar, protic solvents, such as methanol and 2-propanol, gave large amounts of the monoreduced product 6a and some of the fully reduced material 7a. Reaction in ethyl acetate gave the desired C2 product 3a along with the first observation of the formation of the C1 isomer 4a and the monoreduced product 6a. Isomerization in other nonpolar solvents, e.g., hexane, gave similar results. Other aprotic polar solvents, e.g., acetone, dioxane and THF, also largely produced the desired C2 product 3a along with small amounts of the C1 isomer 4a and the monoreduced compound 6a.

We explored whether the isomerization to the C2 isomer in great preference to the C1 isomer was general. The additional di(exo)methylene compounds, 2b−d, were prepared from the corresponding substituted ketones and the bis(chloromethyl)ethylene. Treatment of both 2b and 2c under the conditions described above, namely Pd/C under an atmosphere of hydrogen gas, afforded predominately the C2 products 3b and 3c in preference to the possible C1 product (Scheme 4).

Scheme 4. Isomerization of Alkenes 2bc

However, the diphenyl-substituted analogue 2d gave only starting material under these conditions with no production of any isomer or reduction products. Thus, this preference for the C2 product 3 rather than the C1 product 4 occurs for all alkyl substituents at the bridgehead carbons.

The proposed mechanism is shown in Scheme 5. Coordination of the di(exo)methylene 2 with palladium to give A, hydride addition to form B, β-hydride elimination to afford C, and then decomplexation converts 2 to the monoisomerized product D, which has never been observed. The same type of process can convert D via the intermediates E−H, to either the C2 isomer 3 or the C1 isomer 4 and can interconvert these isomers as well. All processes are reversible, and the product ratio is most likely determined by thermodynamic stabilities.

In order to establish the energies of each of the isomers, we calculated the structures and energies of reactants, the monoisomerized species, and the isomeric di-isomerized species with density functional theory. Using Gaussian 09,10 optimizations were performed using B3LYP/6-31G(d),11 followed by M06-2X/6-311+G(d,p) single-point calculations to account properly for dispersion effects.15 The results are shown in Table 2. The parent unsubstituted system 2 (R = H) shows a 2.9 kcal/mol preference for the C2 isomer over the C1 diene. All the trisubstituted alkenes were significantly more stable than the disubstituted alkene starting materials. Methyl and larger alkyl substituents at the bridgehead carbons led to a greater preference for the C2 isomer. This is in good agreement with the fact that under all conditions the C2 diene 3 is the predominant product.

We set out to investigate the source of the preference for the C2 isomer. As mentioned before, the examination of molecular models revealed a possible unfavorable steric interaction involving the two allylic hydrogen atoms in 4a as shown in Figure 2. Inspection of the optimized geometries reveals that, although the decrease in H⋯H distance correlates well with an increase in stability across the isomers (Figure 3), a 2.28 Å distance is not sufficient to conclude that the 3–4 kcal/mol thermodynamic preference is dominated by steric repulsion.

Table 1. Effect of Solvents on Conversion of 2a to 3a, 4a, 6a, and 7a

| entry | solvent | time (h) | 3a | 4a | 6a | 7a | 2a |
|-------|--------|---------|----|----|----|----|----|
| 1     | MeOH   | 1       | 68 | 0  | 28 | 4  | 0  |
| 2     | iPrOH  | 1       | 68 | 0  | 26 | 6  | 0  |
| 3     | EtOAc  | 1       | 87 | 9  | 4  | 0  | 0  |
| 4     | hexane | 1       | 81 | 7  | 12 | 0  | 0  |
| 5     | acetone| 1       | 79 | 6  | 14 | 0  | 0  |
| 6     | dioxane| 1       | 64 | 6  | 11 | 0  | 19 |
| 7     | THF    | 1       | 77 | 9  | 13 | 0  | 1  |
Interestingly, a twisting of the bicyclo[3.3.1]nonadienone core in 3a, which is not observed in the less stable 4a, points toward ring strain induced by nonbonding interactions as being another component of the energy difference. This slight rotation relieves some of the unfavorable eclipsing interactions and translates to an increase in the endo hydrogen distance.

In summary, the facile isomerization of the di(exo)methylene bicyclo[3.3.1]nonanone systems gives rise predominantly to the C2 products rather than the possible Cs products. Theoretical calculations reveal that the origin of this preference stems from thermodynamics effects, involving transannular hydrogen−hydrogen interactions and ring strain induced by these interactions. Further calculations and the use of this procedure in the synthesis of rugulosone 1 are currently underway and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information
Experimental procedures and proton and carbon NMR for all new compounds, plus the gas-phase geometries and total energies of the structures calculated using the Gaussian program. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Authors
*E-mail: jung@chem.ucla.edu.
*E-mail: houk@chem.ucla.edu.

Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the National Institute of General Medical Sciences, National Institutes of Health GM-36770 (K.N.H.) for financial support of this research. H.V.P. is funded by the UCLA Graduate Division and is a recipient of the NIH Chemistry−Biology Interface Research Training Grant (USPHS National Research Service Award GM-008469). This work used the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by National Science Foundation Grant No. OCI-1053575. This material is based upon work supported by the National Science Foundation under Equipment Grant No. CHE-1048804.

REFERENCES

(1) (a) Davies, S. G. Organotransition Metal Chemistry, Applications to Organic Synthesis; Pergamon Press: Oxford, 1982; pp 266−290.
(b) Colquhoun, H. M.; Holton, J.; Thompson, D. J.; Twigg, M. V. Isomerization of Alkenes. In New Pathways for Organic Synthesis; Springer: New York, 1984; pp 173−193. (c) Casey, C. P.; Cyr, C. R. J. Am. Chem. Soc. 1973, 95, 2248.
(2) (a) Whitesell, J. K. Carbonyl Group Derivatization. In Comprehensive Organic Synthesis; Trost, B. M., Fleming, I., Eds.;
Inoue, S.; Takaya, H.; Tani, K.; Otsuka, S.; Sato, T.; Noyori, R. J. Am. Chem. Soc. 1990, 112, 4897. (c) Otsuka, S.; Tani, K. Synthesis 1991, 665. (d) Corey, E. J.; Suggs, J. W. J. Org. Chem. 1973, 38, 3224. (e) Cherkaoui, H.; Souilhoui, M.; Grée, R. Tetrahedron 2001, 57, 2379. (f) Tanaka, K.; Fu, G. C. J. Org. Chem. 2001, 66, 8177.

Danishefsky, S.; Uang, B. J.; Qualls, G. J. Am. Chem. Soc. 1985, 107, 1285. (b) Larsen, C. R.; Grotjahn, D. B. J. Am. Chem. Soc. 2012, 134, 10357; (Correction) 2012, 134, 15604. (c) Larsen, C. R.; Erdogen, G.; Grotjahn, D. B. J. Am. Chem. Soc. 2014, 136, 1226.

(a) Moses, J. E.; Baldwin, J. E.; Marquez, R.; Adlington, R. M.; Cowley, A. R. Org. Lett. 2002, 4, 3731. (b) Tan, E. H. P.; Lloyd-Jones, G. C.; Harvey, J. N.; Lennox, A. J. J.; Mills, B. M. Angew. Chem., Int. Ed. 2011, 50, 9602. (c) Chen, C.; Dugan, T. R.; Brennessel, W. W.; Weix, D. J.; Holland, P. L. J. Am. Chem. Soc. 2014, 136, 945.

(a) Tkach, V. S.; Suslov, D. S.; Gomboogiin, M.; Ratovskii, G. V.; Shmidt, F. K. Russ. J. Org. Chem. 2009, 75, 85. (b) Lim, H. J.; Smith, C. R.; RajanBabu, T. V. J. Org. Chem. 2001, 66, 8177.

(a) Lee, C.; Yang, W.; Parr, R. G. Phys. Rev. B 1988, 37, 785. (b) Becke, A. D. J. Chem. Phys. 1993, 98, 5648. (c) Parr, R. G. Annu. Rev. Phys. Chem. 1995, 46, 701.

(a) Zhao, Y.; Truhlar, D. G. Acc. Chem. Res. 2008, 41, 157. (b) Zhao, Y.; Truhlar, D. G. J. Phys. Chem. A 2008, 112, 1095.