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HIGHLY STEREOSELECTIVE AXIAL ADDITION OF ETHYNYL CARBANIONS TO THE CARBONYL OF CYCLOHEXENONES

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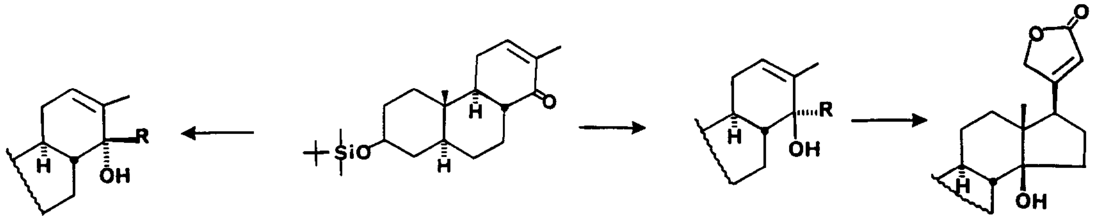
Abstract: This communication reports that highly stereoselective axial addition of ethynyl anions is the normal result with conformationally defined conjugated cyclohexenones, in the absence of overriding steric factors.

We report here that lithium acetylides add stereospecifically in an axial manner to conformationally defined cyclohexenones.[1]

The additions of organometallic reagents to cyclohexenones which have been reported previously have either been non stereoselective or appeared to have been under the control of overriding steric constraints.[2] We were surprised, however, that we could find no study of the addition of acetylides to conformationally defined cyclohexenones,[3] especially since acetylides are known to give moderate to complete axial additions to cyclohexanones.[4,5]

We chose to investigate the problem using tricyclic enone 1[6] because it is a relatively rigid system in which access to either face of the carbonyl is unimpeded, and because the hoped-for axial addition would give us an entry into the 14-β-hydroxysteroid arrangement of the cardenolides (cf 4).

We first showed that the addition of ethyl lithium to 1 is not selective.

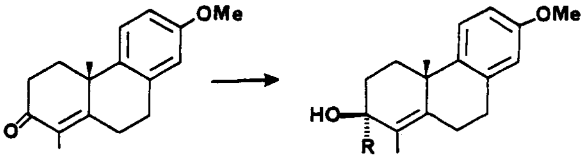


3 1 2 4

At -78°C in THF we obtained an excellent yield of what proved to be a 4:3 mixture of 2 and 3, R = Et. We were, however, pleased to find that addition of the enone 1 to lithium acetylide in THF (2 days at -78°C) led to a crystalline adduct in ~95% yield. This appeared to be a single substance (21 resonances in the ^{13}C NMR spectrum; single vinyl resonance (δ 5.46); one angular and one allylic methyl (δ.773 and 1.84 respectively). The x-ray structure determination[7] of the recrystallized substance, mp 120-121°C (hexane; -10°C), established that it was 2, R = ethynyl.

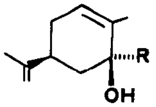
The clean axial addition of the acetylene anion to cyclohexenones at low temperature should be applicable to its homologs: addition of the lithium salt of 1-pentyne gave a single adduct 2, R : C ≡ C - Pr (C = C$\underline{H}$ δ 5.39).

Analogous results were obtained in carbanion additions to the enone 5.[8] Acetylene addition gave only one tertiary alcohol, obviously 6, R = ethynyl. In contrast, addition of ethyl lithium gave, in a 3-1 ratio, both 6, R = ethyl, and its epimer. The predominant isomer was correlated with the sole ethynyl carbinol by hydrogenation of the latter ($(\phi_3P)_3RhCl$, H_2, ϕH). The presence of a vicinal methyl on the double bond does not appear to affect the stereoselectivity: The desmethyl analog of 5 gave evidence of only one adduct with pentynyl lithium.



5 6

The stereoselectivity of acetylide addition which is observed in relatively rigid systems extends to monocyclic cyclohexenones if their conformation is sufficiently unambiguous: (-) carvone gave (lithium acetylide, THF, -78°C) a single ethynylcarbinol (assigned structure 7, R = ethynyl, by analogy) in 95% yield.[9] This was correlated with the predominant isomer 7, R = ethyl, formed together with its epimer (ratio 1.3:1), by addition of ethyl lithium under the same conditions.



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It is clear that the addition to cyclohexenones is a highly axial-selective process. We believe that the axial approach to the carbonyl is due to the continuous overlap of the developing sp^3 orbital with the pi system of the enone that such an approach allows.[10] If there are no substituents bigger than hydrogen in 1, 3 axial relationship to the entering acetylene, steric factors are insufficient to reverse the stereoelectronic advantage.

The addition of acetylide anions to the carbonyl of conjugated cyclohexenones thus appears to be a significant addition to the relatively small number of very highly stereoselective processes available for the formation of carbon-carbon bonds. Whatever the theoretical arguments, the wide variety of transformations which an acetylene can undergo, as well as the possibility of migrating the function to the end of a chain[11], should make the process one of considerable synthetic utility.

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References and Notes:

1. This material is taken, in part, from the Ph.D. Thesis of Jeffrey M. Stryker, Columbia University, 1983.

2. Cf. Adinolfi, M.; Mangoni, L.; Barone, G.; Laonigro, G. Gazz. Chim. Ital. 1973, 103, 1271. Kerekes, P.; Bognar, R.; Gall, G.; Horvath, G. Magy. Kem. Foly. 1973, 79, 401. Trost, B.M.; Keeley, D.E.; Arndt, H.C.; Rigby, J.H.; Bogdanowicz, M.J. J. Am. Chem. Soc. 1977, 99, 3080; Still, W.C. ibid. 1977, 99, 4186.

3. A case of modest axial selectivity in the addition of an acetylide to a flexible cyclohexenone, has been: Kienzle, F.; Mayer, M. Helv. Chim. Acta 1978, 61, 2609.

4. Hennion, G.F., O'Shea, F.X. J. Am. Chem. Soc. 1958, 80, 614. Findlay, J.A.; Desai, D.N.; Lonergan, G.C.; White, P.S. Can. J. Chem. 1980, 58, 2827. For an acetylide addition leading to complete axial entry in a complex cyclohexanone, see Caine, D ; Smith, Jr., T.L. J. Am. Chem. Soc. 1980, 102, 7568.

5. With cyclohexanone systems, some of the theoretical considerations relevant to the question of axial vs equatorial addition have been examined, inter alios, by Felkin (Cherest, M.; Felkin, H.; Prudent, N. Tetrahedron Lett. 1968, 2199. Cherest, M.; Felkin, H. Tetrahedron Lett. 1968, 2205. Cherest, M. Tetrahedron, 1980, 36, 1593), as well as by Anh (cf Anh, N.T. in "Topics in Current Chemistry" 1980, 88, 145) and by

Cieplak, A.S. (J. Am. Chem. Soc. 1981, 103, 4540). See also Ashby, E.C. Laemmle, J.T. Chem. Rev. 1975, 75, 521.

6. The enone 1 was prepared either de novo as the ± isomer from an appropriate tricyclic enone (Stork, G.; Meisels, A.; Davies, J.E. J. Am. Chem. Soc. 1963, 85, 3419) or in optically active form, from ergosterol. Details are in the Ph.D. thesis of J. M. Stryker[1].

7. The analysis of the x-ray data was carried out by Professor L. Lessinger of Barnard College. The crystallographic data are being reported separately by him.

8. Ogiso, A.; Pelletier, S.W. Chem. Commun. 1967, 94.

9. Simple cyclohexenones are of course easily distorted and predictions must be made with some caution: it is not surprising that the presence of an adjacent equatorial isopropyl group in piperitone leads to very slow addition at -78°C. At ~-40°C, addition required ~40 h and the ratio was only 1.3 to 1 in favor of the axial adduct.

10. Toromanoff, E. in "Topics in Stereochemistry" 1967, 2, 157. For a somewhat different point of view, see Baldwin, J.E., J. Chem. Soc., Chem. Commun. 1976, 738.

11. Brown, C.A.; Yamashita, A. J. Am. Chem. Soc. 1975, 97,891. Application to alkynyl carbinols: Hommes, H.; Brandsma, L. Recl. Trav. Chim. Pays Bas 1977, 96, 160; Midland, M.M.; Halterman, R.L.; Brown, C.A.; Yamaichi, A. Tetrahedron Lett. 1981, 4171.

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