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# A FACILE PREPARATION OF DIFFERENTIATED 1,2-DIVINYLCYCLOALKANOLS

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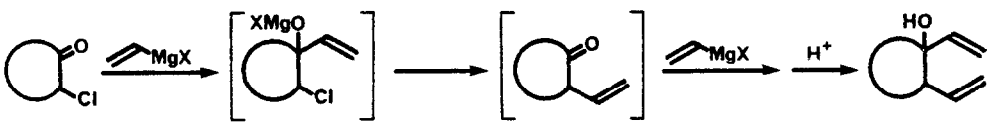
Abstract: A method is described which permits one-step conversion of 2-chlorocycloalkanones to differentiated 1,2-divinylcycloalkanols, 2-vinylcycloalkanones, or 2-vinylcycloalkanols.

The oxy-Cope rearrangement[2] provides the basis for a particularly attractive approach to medium and large ring natural products from more readily available small ring precursors.[3] However, preparation of the 1,2-divinylcycloalkanols required in this ring expansion technique usually involves several steps[3b,c,e,f] or demands appropriately substituted natural product precursors.[3d] Our interest in this particular ring expansion methodology has prompted an investigation of a more efficient preparation of 1,2-divinylcycloalkanols, based on the addition of differentially substituted vinyl groups to 2-chlorocycloalkanones. Our studies on this method and its extensions, which provide for equally facile preparation of 2-vinylcycloalkanones and 2-vinylcycloalkanols, are described herein.

Our approach is based on the well known pinacol-like rearrangements of arylchlorohydrins,[4] and the analogous vinyl migration first observed[5] in the divinylation of 2-chlorocyclododecanone. The mechanism for the latter is proposed to involve initial 1,2-addition of the vinyl Grignard to the α-chloroketone, followed by a vinyl group migration. The resulting α-vinylketone is then attacked by excess vinyl Grignard to yield the 1,2-divinylcyclododecanone (Scheme I).

**Scheme I**




Clearly, the ability to introduce differentially substituted vinyl groups in one operation would allow greater control over the type and position of peripheral appendages in the ring expanded products as required for natural product synthesis. The method developed in these laboratories to efficiently accomplish this goal involves treatment of a chlorcketone (1) in THF with one equivalent of a first vinyl Grignard (2) at 0°C for

two hours to effect 1,2-addition. A second vinyl Grignard (3) is then added, and the solution is heated at reflux for three hours, in order to effect rearrangement and subsequent 1,2-addition to the intermediate ketone. Aqueous workup followed by column chromatography affords the divinylcycloalkanol 4 (Scheme II).

**Scheme II**

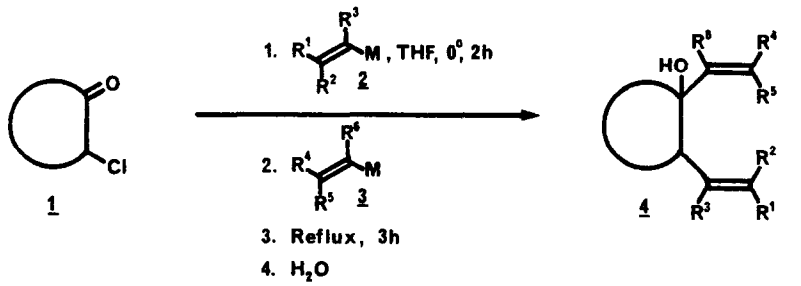



Table I summarizes some of the cases investigated. It is noteworthy that: (i) vinyllithium reagents, as well as Grignard reagents, can be utilized (cf. 1a → 4a, 1b → 4b); (ii) bromoketones can be used in place of chloroketones,[6] although this results in lower yield[7] (1c → 4c); (iii) tertiary chlorides also undergo rearrangement, thereby providing a means of generating a quaternary carbon center[8] adjacent to the original carbonyl (1e → 4e); and (iv) six and seven membered rings can be used (1d → 4d).[9]

The expectation that this methodology could be extended to accommodate other nucleophiles as alternatives to the second vinyl Grignard proved to be reasonable as was demonstrated by using methyl Grignard (1h → 4h). Of special interest is the use of hydride as the second nucleophile leading to the α-vinylated secondary alcohol (1i → 4i). This has the advantage over vinyllithium induced epoxide cleavage for the preparation of 2-vinylcycloalkanols in that it avoids use of the less practical alkenyllithium reagent and the possible non-regiospecificity of the epoxide opening.

Another important variation on this theme is the α-vinylation of ketones -- typically a laborious multi-step task.[10] The α-vinylketone intermediate in the above sequence (Scheme I) is easily isolable in good yield when the second nucleophile is omitted altogether (1j → 4j).[11]

Thus, a very convenient and efficient procedure for preparation of 2-vinylcycloalkanones and 2-vinylcycloalkanols, as well as mixed-1,2-divinylcycloalkanols, has been realized. Further studies on the scope and applications of this method are in progress.

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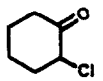
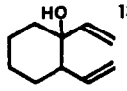
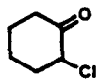
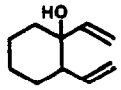
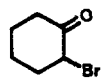
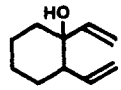
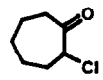
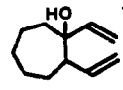
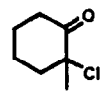
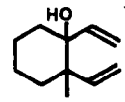
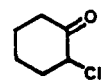
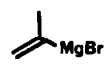
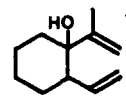
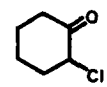
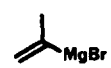
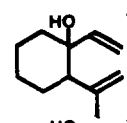
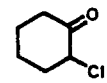
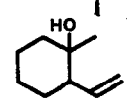
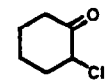
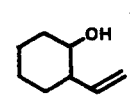
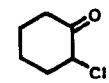
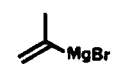
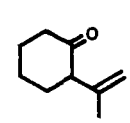
TABLE 1

| Entry | 1 | 2 | 3 | 4 | %Yield[a] | Cis/Trans[b] |
|---|---|---|---|---|---|---|
| a |  |  |  |  13a | 69 | 85/15 |
| b |  |  |  |  | 57 | 85/15 |
| c |  |  |  |  | 36 | 85/15 |
| d |  |  |  |  14,15 | 61 | |
| e |  |  |  |  16 | 60 | |
| f |  |  |  |  17 | 63 | 90/10 |
| g |  |  |  |  18 | 52 | 90/10 |
| h |  |  | CH,MgBr |  13b | 63 | 90/10 |
| i |  |  | LiAlH$_4$ |  13b | 67 | 50/50[c] |
| j |  |  | |  19 | 56[d] | |

[a] Yields are those isolated after flash column chromatography[12] and are not optimized.

[b] Determined by GC (3% OV-210, 20'x 1/8", 100°). Cis and trans refer to relative positions of hydroxy and α-vinyl groups.

[c] Determined by GC (3% SE-30, 20'x 1/8", 90°).

[d] Determined by GC.

References and Notes


1. National Institutes of Health Training Grant recipient, 1980-1981.
2. For a review of the oxy-Cope rearrangement see S.J. Rhoads and N.R. Raulins, Org. React., 22, 61 (1975). See also D.A. Evans and A.M. Golob, J. Am. Chem. Soc., 97, 4765 (1975), and D.J. Baillargeon, Ph.D. Thesis, California Institute of Technology, 1979 as leading references to the anion-accelerated oxy-Cope.
3. (a) E. Brown, P. Leriverend and J.M. Conia, Tetrahedron Lett., 6115 (1966); (b) E.N. Marvell and W. Whalley, Tetrahedron Lett., 509 (1970); (c) R.C. Cookson and P. Singh, J. Chem. Soc., (c), 1477 (1971); (d) W.C. Still, J. Am. Chem. Soc., 99, 4186 (1977); (e) W.C. Still, J. Am. Chem. Soc., 101, 2493 (1979); (f) M. Kahn, Tetrahedron Lett., 4547 (1980).
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5. M. Nishino, H. Kondo and A. Miyake, Chem. Lett., 667 (1973).
6. The magnesium vinylbromohydrin was observed to undergo rearrangement at room temperature, whereas temperatures in excess of 50° were necessary for rearrangements of the magnesium vinylchlorohydrins.
7. Lower yields for the rearrangements of arylbromohydrins relative to arylchlorohydrins have also been observed.[4f]
8. For a recent review of construction of quaternary carbon centers see: S.F. Martin, Tetrahedron, 36, 419 (1980).
9. During completion of this study, a complementary paper dealing with divinylations of various size 2-chlorocycloalkanones appeared in the literature: T. Kato, H. Kondo, M. Nishino, M. Tanaka, G. Hata and A. Miyake, Bull. Chem. Soc. Jpn., 53, 2958 (1980).
10. For two recent papers on α-vinylations of ketone enolates see: T.C.T. Chang, M. Rosenblum and S.B. Samuels, J. Am. Chem. Soc., 102, 5930 (1980); C.J. Kowalski and J. Dung, J. Am. Chem. Soc., 102, 7950 (1980).
11. The use of THF as solvent for this monovinylation resulted in low yields of the desired ketone and isolation of significant amounts of the non-rearranged vinylchlorohydrin, even after prolonged heating. Presumably deprotonation of the vinylketone product by the intermediate alkoxide served to stop rearrangement of the chlorohydrin. This problem was largely alleviated by using benzene as solvent.[5]
12. W.C. Still, M. Kahn and A. Mitra, J. Org. Chem., 43, 2923 (1978).
13. Spectral data were consistent with that previously reported. (a) E.N. Marvell and W. Whalley, Tetrahedron Lett., 509 (1970); (b) E.N. Marvell and R. Rusay, J. Org. Chem., 42, 3336 (1977).
14. All new compounds gave satisfactory IR, NMR and mass spectra and exact mass and/or combustion analyses.
15. 4d: NMR($CDCl_3$) δ 1.1-2.1(m,11H), 2.2(bt,J~7Hz,1H), 4.8-6.2(m,6H); IR($CCl_4$) 3590, 1640, 1000, 925 $cm^{-1}$.
16. 4e: NMR($CDCl_3$) δ 1.02,1.07(s,3H), 1.40(s,1H), 1.58(bs,8H), 4.85-5.4(m,4H), 5.85-6.35 (m,2H); IR($CCl_4$) 3620, 1635, 1000, 970, 925 $cm^{-1}$.
17. 4f(cis): NMR($CDCl_3$) δ 1.3-1.9(m,8H), 1.42(s,1H), 1.78(dd,$J_a+J_b$=1.9Hz,3H), 2.25-3.0 (bq,J~7Hz,1H), 4.7-5.2(m,4H), 5.6-6.0(m,1H); IR($CCl_4$) 3600, 1630, 975, 920 $cm^{-1}$; 4f(trans): NMR($CDCl_3$) δ 1.1-2.1(m,8H), 1.29(s,1H), 1.76(s,3H), 2.3-2.55(m,1H), 4.7-5.2(m,4H), 5.55-6.05(m,1H); IR($CCl_4$) 3600, 1640, 910 $cm^{-1}$.
18. 4g(cis): NMR($CDCl_3$) δ 1.1-2.2(m,10H), 1.75(dd,$J_a+J_b$=2.3Hz,3H), 4.65-5.3(m,4H), 5.9 (dd,$J_a+J_b$=27.6Hz,1H); IR($CCl_4$) 3580, 1640, 975, 920 $cm^{-1}$; 4g(trans): NMR($CDCl_3$) δ 1.2-1.9(m,8H), 1.67(s,3H), 2.17(s,1H), 2.1-2.4(m,1H), 4.7-5.45(m,4H), 6.40(dd,$J_a+J_b$= 27.9Hz,1H); IR(neat) 3560, 1640, 980, 920 $cm^{-1}$.
19. 4j: NMR($CDCl_3$) δ 1.4-2.2(m,6H), 1.75(s,3H), 2.2-2.5(m,2H), 2.8-3.1(m,1H), 4.65-4.75 (m,1H), 4.85-4.95(m,1H); IR(neat) 1710, 1650, 895 $cm^{-1}$.


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