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A FACILE ROUTE TO MACROCYCLIC KETONES.
DIRECT DIVINYLATION OF 2-CHLOROCYCLODODECAN-1-ONE

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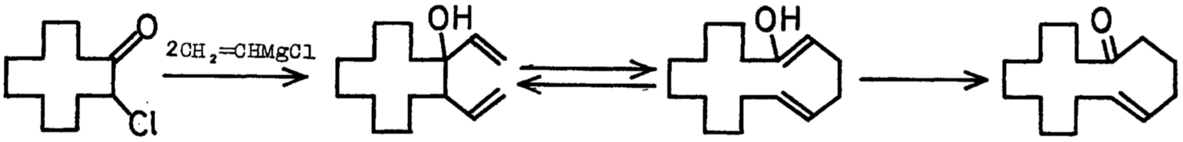
The reaction of 2-chlorocyclododecan-1-one with vinylmagnesium chloride (molar ratio at 1:2) gave directly 1,2-divinylcyclododecan-1-ol, which was easily converted to 5-cyclohexadecen-1-one. This one-step divinylation was found to proceed not through a direct displacement of the Grignard reagent with the chlorine atom, but through a pinacol-like rearrangement of a vinyl group.

The oxy-Cope rearrangement has enabled the preparation of macrocyclic ketones from accessible medium-ring compounds.1) In this communication we describe a facile method for preparing 1,2-divinylcyclododecan-1-ol (I), which is readily converted into 5-cyclohexadecen-1-one (II) via the rearrangement. This method is simpler than the one reported by Marvell and Whally.2)

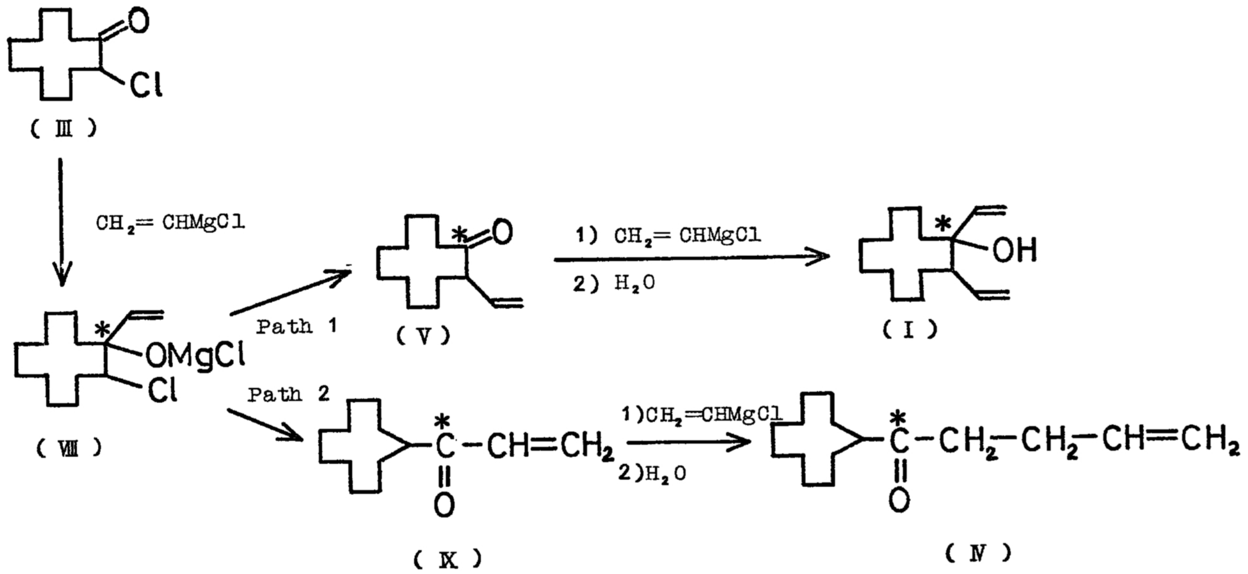


(III) (I) (II)

One mole of 2-chlorocyclododecan-1-one (III) was treated with two moles of vinylmagnesium chloride in tetrahydrofuran at 0℃, and the reaction mixture was stirred at 55℃ for 15 hours. After hydrolysis and distillation, the reaction product was analyzed by gas chromatography (2m, Silicone SE on Celite 545, at 230℃). It consisted of 55% of cis- and trans-1,2-divinylcyclododecan-1-ols (I)$^{3)}$ [trans isomer (40%): mp 51~52℃; ir (KBr), 3420, 1640, 997, 980, 918, 906cm^{-1}; nmr (CCl$_4$, 100MHz), δ 4.7~6.0 (ABX type, 6H), 2.12 (t,1H); mass, 236 (M$^+$); cis isomer (60%): mp 15~16℃; bp 122~123℃/0.7mmHg; n_D^{20} 1.5023; ir (neat), 3550, 1638, 998, 920cm^{-1}; nmr (CCl$_4$, 100MHz), δ 4.9~6.0 (ABX type, 6H), 2.3 (t, 1H)], 2% of 1-cycloundecyl-4-penten-1-one (IV) [bp 116~118℃/0.3mmHg; n_D^{25} 1.4873; ir (neat), 1710, 1640, 995, 910cm^{-1}; nmr (CCl$_4$, 100MHz), δ 4.8~6.0 (ABX type, 3H); mass, 236 (M$^+$)], and 43% of a mixture of 2-vinylcyclododecan-1-one (V) [bp 80~84℃/0.2mmHg; n_D^{25} 1.4943; semicarbazone, mp 182~184℃; ir (neat), 1710, 1635, 990, 915cm^{-1}; nmr (CCl$_4$, 100MHz), δ 4.9~6.0 (ABX type, 3H); mass, 208 (M$^+$)] and 2-ethylidenecyclododecan-1-one (VI) [bp 103℃/0.7mmHg; mp 29~31℃; semicarbazone, decompd. at 234℃; ir (neat), 1665, 1640cm^{-1}; nmr (CCl$_4$, 60MHz), δ 6.6 (quartet, J=9.8Hz, 1H), 1.85 (d, J=9.8Hz, 2H); mass, 208 (M$^+$)]. Subsequent heating of the whole for 1 hour at 190℃ produced 5-cyclohexadecen-1-one (II) [a mixture of cis (40%) and trans (60%) isomers: bp 121℃/0.1mmHg; n_D^{25} 1.4865; semicarbazone, mp 179.5~181.5℃; ir (neat), 1710, 1660, 970, 710cm^{-1}; nmr (CCl$_4$, 60MHz), δ 5.1~5.3 (m, 2H); mass, 236 (M$^+$)], in ca. 40% yield from (III).

The ketone (II) was identified by converting to the known$^{5)}$ cyclohexadecan-1-one (mp 60℃; semicarbazone, mp 185.5~187℃) by hydrogenation. Ozonolysis and subsequent oxidation with potassium permanganate gave 1,12-dodecanedioic acid, 1,11-undecanedioic acid, and sebacic acid, but no higher dicarboxylic acids. This shows that the ketone (II) possesses an olefinic double bond between C-5 and C-6. The ketone (IV) with an eleven-membered ring was identified by comparing its refractive index, mass, ir, and nmr spectra with those of an authentic sample synthesized from cycloundecanecarboxylic acid and a large excess of vinylmagnesium chloride.$^{6)}$

The divinylation of the α-chloroketone (III) proceeds through a vinyl group rearrangement as described below. This rearrangement takes place at a temperature higher than 50℃.



The reaction of (III) with vinylmagnesium chloride below room temperature gives 2- chloro-1-vinylcyclododecan-1-ol (VII).[7] but no product formed by the displacement reaction of the Grignard reagent with the chlorine atom.[8] The 1,2-migration of a vinyl group of the chloromagnesium derivative (VIII) proceeds at higher temperatures and forms an intermediate 2-vinylcyclododecan-1-one (V), which reacts further <u>in situ</u> with vinylmagnesium chloride, producing 1,2-divinylcyclododecan-1-ol (I), (path 1). On the other hand, the migration of an alternate group on the C-2 position of the chlorohydrin derivative (VIII), (path 2), leads to a ring contraction, yielding 1-cycloundecyl-2-propen-1-one (IX), which in turn gives 1-cycloundecyl-4-penten-1-one (IV) through 1,4-addition of vinylmagnesium chloride. In the absence of vinylmagnesium chloride, (VIII) gives 81% of (V) and 2% of (VI) at 70 ℃ in a mixture of ether and benzene. This shows that the migratory aptitude of a vinyl group is remarkably superior to that of alkyl groups.[9]

The procedure described here will provide a facile divinylation and a novel synthesis of useful macrocyclic ketones.

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3) The structure of the geometrical isomers was identified by considering the steric cource of the transition state in the oxy-Cope rearrangement[4]: the _trans_ isomer of (I) gave the _trans_ isomer of (II) as the sole product, and the _cis_ isomer of (I) afforded a mixture of the _cis_ and the _trans_ isomer of (II) in the ratio _ca_. 3:1.

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7) The compound (VII) was a mixture of _cis_ and _trans_ chlorohydrin. _Cis_ isomer was the major component: _cis_ isomer: mp 63~65 ℃; ir (KBr), 3550, 3420, 1640, 768cm^{-1}; nmr ($CDCl_3$, 100MHz), δ 5~6 (ABX type, 3H), 4.0 (d, 1H); _trans_ isomer: mp 54~55.5 ℃; ir (KBr), 3550, 1640, 1172, 1118, 758cm^{-1}; nmr ($CDCl_3$, 100MHz), δ 5~6 (ABX type, 3H), 4.2 (d, 1H).

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9) There are, to our knowledge, no reports on the vinyl migration of this kind. On aryl Grignard reagents, aryl groups with higher electron-donating substituents were proved to have a higher tendency to undergo the migration on the halomagnesium derivatives of halohydrins.[10]

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