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AN EFFICIENT, HIGHLY REGIOSELECTIVE SYNTHESIS OF SUBSTITUTED (1-CYCLOHEXENYL) ACETIC ACID DERIVATIVES VIA IONIZATION/ELIMINATION OF ß-LACTONES

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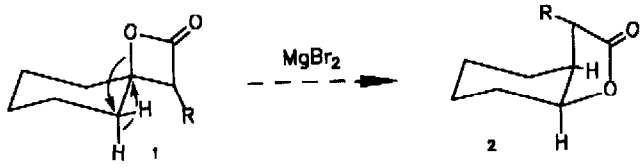
When treated with magnesium bromide, spiro ß-lactones undergo an ionization/elimination reaction to afford cyclohexenyl acetic acid derivatives in high yield and isomeric purity.

Cyclohexenyl acetic acid derivatives occupy a position of some importance in organic chemistry, both as synthetic precursors and as target molecules in their own right. The most common example of the former is their use as cyclization substrates via halo- or selenolactonizations,[1] vinylogous Wolff rearrangements,[2] cycloadditions,[3] etc., but such moieties have also been converted to 2,4-dialkyl-2-cycloalkenyl butyrolactones[4] and into such natural products as mintlactone and isomintlactone.[5] α-Substituted cyclohexenyl acetic acids have also served commercially as precursors to insecticides[6] and as antirust/antiwear compounds.[7]

These molecules are typically prepared via a nucleophilic attack on cyclohexanone, followed by dehydration of the resulting ß-hydroxy ester or acid.[8] A significant problem lies in the low regioselectivity of the latter process, in which the conjugated alkene is often formed as a major product. This is especially true if the α-substituent is aromatic or provides a similar conjugative driving force.[9] In these cases, deconjugation must be effected as a separate step.

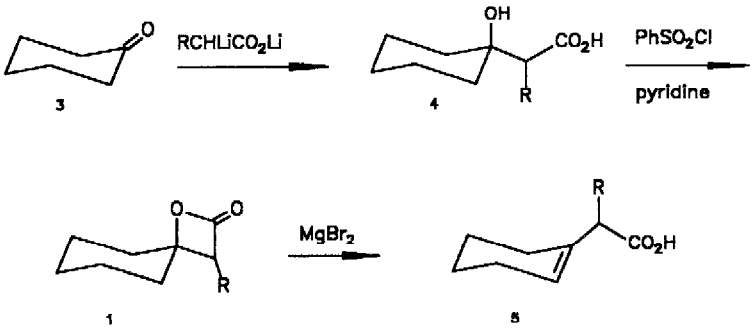
We have recently been engaged in an investigation of organic dyotropic rearrangements as a tool for butyrolactone synthesis.[10] In an effort to prepare cis-fused lactones such as 2, we prepared the ß-lactone 1 (R = Ph), which we had judged an ideal candidate for rearrangement due to the diaxial orientation of the lactone ring oxygen and a ring proton. However, when



exposed to magnesium bromide etherate, the catalyst of choice for such reactions, the molecule was transformed instead into (1-cyclohexenyl)phenylacetic acid (5, R = Ph)[11] in 74% yield.

This reaction appears to be general for substituted spiro ß-lactones. The reaction sequence is outlined in the Scheme, and yield data are collected in the Table. Cyclohexanone (3) was allowed to react with substituted acetic

SCHEME



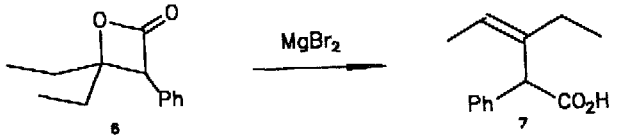
acid dianions (from the acid and two moles of LDA), and the resulting ß-hydroxy acids 4 were dehydrated with benzenesulfonyl chloride in pyridine. The resulting spiro ß-lactones 1, when exposed to magnesium bromide in ether for six hours, provided the indicated acids (5). The yields (unoptimized) are collected in the Table. In no case was any conjugated alkene detected.

Table

Yield Data for Substituted (1-Cyclohexenyl) Acetic acid Synthesis

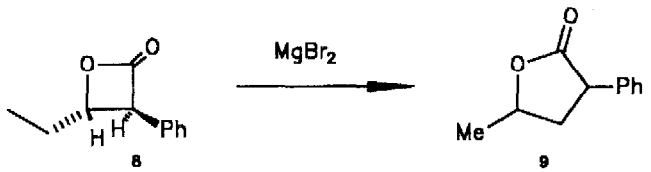
Suffix	R	Yield of 4	Yield of 1	Yield of 5
a	methyl	63	96	99
b	phenyl	95	80	74
c	phenoxy	77	77	99
d	thiophenyl	84	74	80
e	1-naphthyl	60	40	93
f	p-methoxyphenyl	92	84	92

The possible reasons behind this unexpected development are most intriguing. It occurred to us that the ring hydrogen, which we had anticipated would migrate, was perhaps "tied back" by virtue of the cyclohexane ring, resulting in an unacceptably strained transition state for this concerted rearrangement. To test this hypothesis, spiro ß-lactone 6 was prepared (from 3-pentanone, employing the chemistry depicted in the Scheme) and treated with $MgBr_2$, whereupon the unsaturated acid 7 was formed in 98% yield.



6 7

Since the related ß-lactone 8 is known to rearrange to the butyrolactone 9,[10b]



8 9

it seems at this point that the differentiating criterion is the tertiary carbocation which can form upon ionization of spiro ß-lactones. Evidently, if the development of such an intermediate is possible, the adjacent proton is lost (to form an alkene bond) rather than migrating to the tertiary center. Participation by the ether solvent in proton removal is probably not important, since the reaction occurs with equal facility in nonbasic solvents such as dichloromethane. The operative base is thus most likely the carboxylate anion formed during lactone ionization; whether this is an intra- or intermolecular process remains to be determined. These mechanistic points are currently being examined in detail with more discriminating substrates.

In summary, we have developed a rapid, efficient method for the synthesis of substituted (1-cyclohexenyl) acetic acids which produces none of the conjugated isomers. As indicated by the formation of 7, the method should be applicable to acyclic cases as well; this extension is under active scrutiny.

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11. Physical data for 5b: mp 80-81 °C; IR (KBr) 3088, 3083, 2988, 1697, 1220, 700 cm^{-1}; 500 MHz ^{1}H-NMR ($CDCl_3$) δ 7.60-7.00 (m, 5H, ArH); 5.65 (s, 1H, =CH); 4.27 (s, 1H, PhCH); 2.30-1.51 (m, 8H, CH_2); ^{13}C-NMR ($CDCl_3$) δ 178.4, 136.9, 134.9, 129.0 (2C), 128.4 (2C), 127.5, 125.6, 58.9, 27.6, 25.5, 22.9, 22.1; TLC (EtOAc) R_f 0.26.

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