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# REGIO- AND DIASTEREOSELECTIVITY OF ENOL ETHER FORMATION BY 1,4-SIGMATROPIC SHIFTS OF HYDROGEN IN CARBONYL YLIDES

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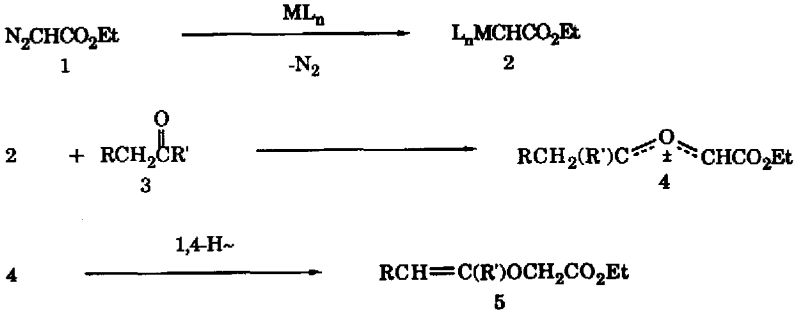
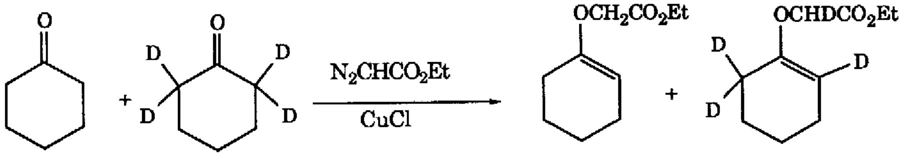
**Summary:** Treatment of aliphatic ketones with ethyl diazoacetate in the presence of a catalyst results in the regio- and (where appropriate) diastereoselective formation of enol ethers which arise by an intramolecular 1,4-hydrogen shift from an intermediate carbonyl ylide.

Since our original observations that the enol ethers produced as a result of CuCl catalyzed decomposition of ethyl diazoacetate in the presence of 2-methylcyclohexanone and 3-methyl-2-butanone were formed with a high degree of regioselectivity,[1] we have determined both the regioselectivity and diastereoselectivity in a number of unsymmetrical acyclic ketones and have developed a mechanistic model to explain the results. The reactions outlined in Scheme I provide the opportunity to explore many mechanistic features of the comparatively rare 1,4-sigmatropic shift of hydrogen.[2-4] The initial production of carbenoid **2** from catalyzed decomposition of ethyl diazoacetate (**1**),[5] followed by electrophilic attack on ketone **3** and 1,4-sigmatropic shift of hydrogen, leads to the product enol ether(s).

**Scheme I**



We have shown that the latter process is indeed an intramolecular event by the observation that an excess equimolar mixture of ketones **6** and **7** results in only undeuterated enol ether **8** and specifically tetradeuterated enol ether **9** with a ratio of 0.96 ±0.05[6]



6 + 7 → 8 + 9

All of the results reported in Tables I and II are the same whether the catalytic decomposition is by CuCl (75 °C, heterogeneous conditions) or by $Rh_2(OAc)_4$ (20-25 °C, homogeneous conditions). Isolated yields of the combined enol ethers are in the range 25-40%.[7]

Table I. Enol Ether Product Distribution for Selected Aliphatic Ketones[a]

| Ketone | Less Subst. Prod. | | | More Subst. Prod. | |
|---|---|---|---|---|---|
| | (E) | (Z) | N.A.S.[b] | (E) | (Z) |
| $CH_3COCH_2CH_3$ (**10**) | - | - | 74-76 | 20-22 | 3-4 |
| $CH_3COCH_2CH_2CH_3$ (**11**) | - | - | 74-75 | 22-23 | 4-5 |
| $CH_3COCH_2CH(CH_3)_2$ (**12**) | - | - | 76-77 | 23-24 | |
| $CH_3COCH(CH_3)_2$ (**13**) | - | - | 100 | 0 | 0 |
| $CH_3CH_2COCH(CH_3)_2$ (**14**) | 100 | 0 | | 0 | 0 |
| $(CH_3)_2CHCOCH(CH_3)_2$ (**15**) | - | - | 100[c] | - | - |

[a] Expressed as a percent of all enol ethers; a 7-fold excess of liquid ketone served as solvent; results are for at least three runs per ketone.

[b] No applicable stereochemistry.

[c] Only a single enol ether is possible.

Table II. Enol Ether Distribution for Selected Benzylic Ketones[a]

| Ketone | Non-conjugated Prod. | | | Conjugated Prod. | |
|---|---|---|---|---|---|
| | (E) | (Z) | N.A.S.[b] | (E) | (Z) |
| $CH_3COCH_2Ph$ (**16**) | - | - | 45-47 | 53-55 | 0 |
| $CH_3COCH(CH_3)Ph$ (**17**) | - | - | 83-85 | 15-17 | 0 |
| $CH_3CH_2COCH_2Ph$ (**18**) | 30-37 | 0 | | 63-70 | 0 |
| $PhCH_2COCH_2Ph$ (**19**) | - | - | | 100 | 0 |

[a] Expressed as a percent of all enol ethers; for liquid ketones, a 7-fold excess served as the solvent; for solid ketones, a 6-fold excess was dissolved in $CCl_4$; results are for at least three runs per ketone.

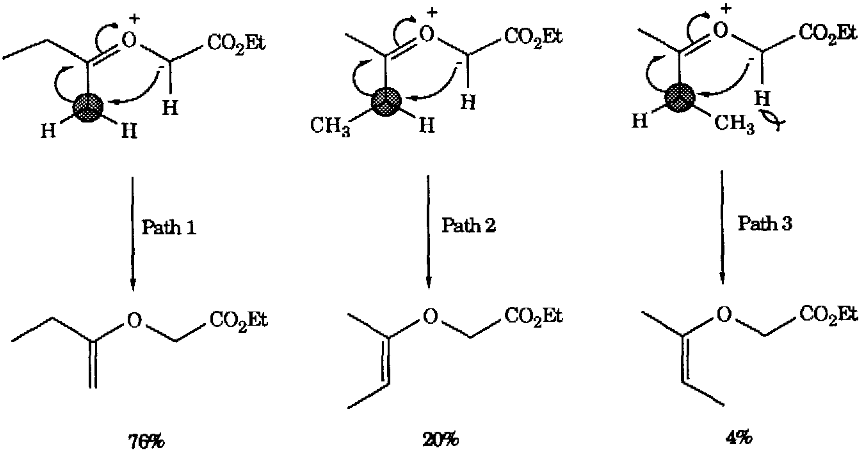
[b] No applicable stereochemistry.

A glance at Table I clearly indicates that the 1,4-sigmatropic hydrogen migration preference is $CH_3 > CH_2 >> CH$. Thus, enol ether formation toward methyl is favored in these alicyclic systems by about 3-fold relative to enol ether formation toward methylene. Hydrogen migration from a tertiary center is not observed unless, as with diisopropyl ketone (**15**), there is no other choice. In the latter case, the isolated yield is about 25%. The results in Table II show that the regiochemical preference for the least substituted enol ether is somewhat reduced when the more substituted enol ether is conjugated with an aromatic ring.

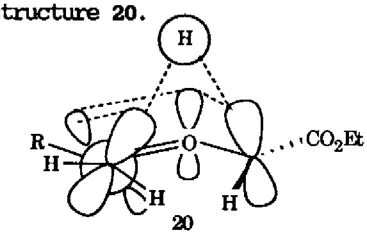
Of equal mechanistic significance are the data from both tables which show that there is a considerable diastereoselectivity observed when an enol ether can be formed as an (E)- or (Z)-isomer. The (E)-isomer, confirmed by suitable NOE experiments, is always the dominant or exclusive product. Even with ethyl isopropyl ketone (**14**), the (E)-isomer in which methyl and isopropyl are *cis*, is the only product observed.

Both the regio- and diastereoselectivities observed can be readily accommodated by considering various reasonable starting configurations and conformations for the essentially planar carbonyl ylide in which the C-H bond of the migrating hydrogen is approximately perpendicular to the plane of the ylide. Scheme II outlines such starting structures for the carbonyl ylide derived from methyl ethyl ketone (**10**).

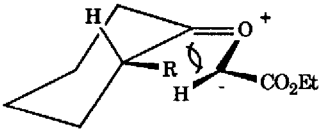
**Scheme II**



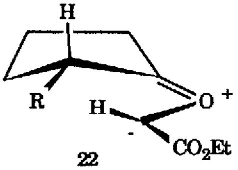
As the hydrogen (represented by the shaded circle) begins to migrate, the hybridization of the carbon atom at the origin for migration shifts toward $sp^2$, and steric interactions between endo-oriented, non-migrating groups at each end of the 1,4-system increase. As long as these groups are hydrogen atoms, as depicted in paths **1** and **2**, this interaction is not significant. Note that the interaction which develops in the transition state for path **3** disfavors the formation of the (Z)-isomer. Because there are three equally probable methyl rotamers corresponding to the starting conformation for path **1**, but only one such rotamer for path **2**, the observation that enol ether formation toward methyl is favored by a factor of approximately three over enol ether formation toward methylene (with production of the (E)-isomer) is qualitatively accommodated. An orbital picture which provides a better representation of the relationship among various groups during the migration of hydrogen is shown below as structure **20**.



**20**



**21**



**22**

Cyclic ketones display a regioselectivity for enol ether formation which depends on ring size. For example the ratio of less to more substituted enol ether from 2-methylcyclohexanone is 12-13:1,[1] while for 2-methylcyclopentanone it is only 5-7:1. The same model described above, but modified to account for the difference in ring conformations leads to structures **21** and **22** which suggest a larger steric interaction developing during the formation of the more substituted enol ether in 2-methylcyclohexanone. 2-Phenylcyclohexanone results in a ratio of less- to more-substituted enol ether of only 1.5:1 while for 2-phenylcyclopentanone this ratio is only 1.3:1, consistent with the expected effects of conjugation.

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6. That the product ratio is within experimental error of 1.0 provides evidence that carbonyl ylide formation is not appreciably reversible.
7. Structures of newly prepared enol ethers were identified by a combination of $^1$H and $^{13}$C-NMR, IR, and MS (including an exact mass).

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