Acid-catalysed Thermal Rearrangement of γ,δ-Unsaturated Ketones

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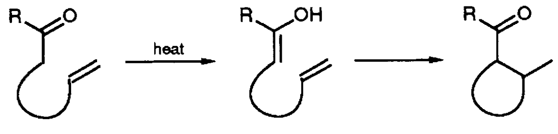
Thermal activation of γ,δ-unsaturated ketones (**1**, **9** and **12**) in the presence of a catalytic amount of propionic acid causes a rearrangement to give new γ,δ-unsaturated ketones (**2**, **10** and **14**) *via* an intramolecular ene reaction followed by a retro-ene reaction.

Thermal cyclisation of unsaturated carbonyl compounds to give a variety of normal- (including bridged and spiro systems) and medium-sized rings can be achieved *via* an intramolecular ene reaction, provided the geometry of the system favours a six-electron cyclic process involving the participation of the



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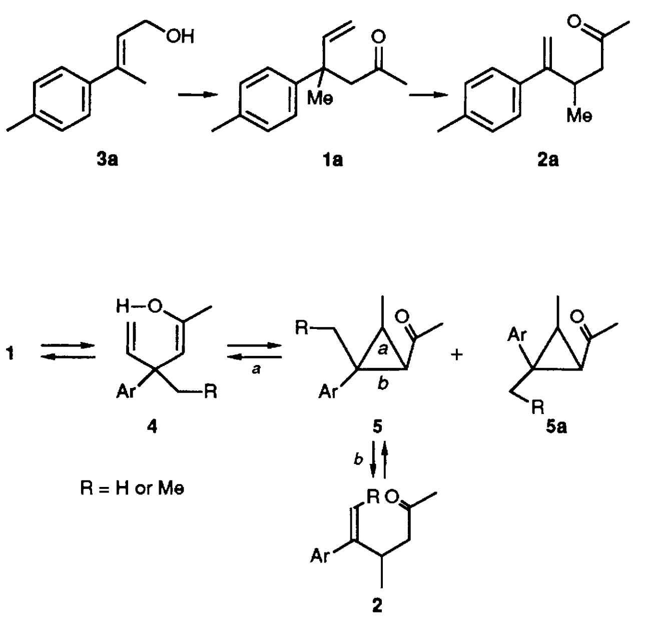


Scheme 1

enol intermediate and the alkene moiety [eqn. (1)].[1] On the other hand, small rings cannot be generated in an analogous manner as the reverse reaction will be more facile because of the strain.[1] However, by a suitable design, the forward reaction and an alternate reverse reaction may bring about rearranged systems. Based on this concept, herein we report a novel transformation of γ,δ-unsaturated ketones to isomeric systems by an acid-catalysed thermal reaction.[2]

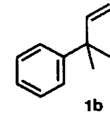
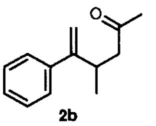
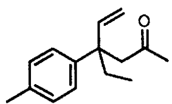
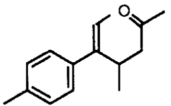
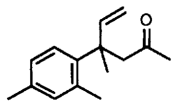
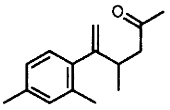
Thermal activation of the enone[3] **1a** in toluene, in the presence of a catalytic amount of propionic acid, in a sealed tube at 250 °C for 48 h generated a 2 : 1 mixture of the rearranged enone **2a** and the starting enone **1a**. Alternatively, reaction of the cinnamyl alcohol **3a** in toluene and 2-methoxypropene in the presence of a catalytic amount of propionic acid at 230–250 °C for 48 h furnished the same mixture of the enone **2a** and the normal Claisen product **1a**. The structure of the rearranged enone **2a** was deduced from its spectral data (UV, IR, ^1H and ^{13}C NMR, mass). In particular the presence of typical *gem* disubstituted olefinic signals [5.18 (1 H, s) and 5.0 (1H, s)] and a typical $AMNX_3$ spin pattern [δ 3.1–3.7 (1 H, m), 2.65 (1 H, d of ½AB q, *J* 16, 5 Hz), 2.4 (1 H, d of ½AB q, *J* 16, 9 Hz) and 1.15 (3H, d, *J* 7 Hz)] for the $Me–CH–CH_2–C{=}O$ moiety in the ^1H NMR spectrum clearly established the structure of the rearranged enone **2a**.

The formation of the enone **2a** can be explained as depicted in Scheme 1. An intramolecular ene reaction of the enol tautomer **4** of the enone **1a**, provides the cyclopropyl ketones **5**. A retro-ene reaction (or a 1,5 hydrogen transfer) of the cyclopropyl ketone **5**, generates either the starting enone **1a** or the rearranged enone **2a** *via* the cleavage of the cyclopropane bonds either *a* or *b*, respectively. Whereas the alternate stereoisomer **5a** reverts to the starting enone **1a**.

The generality of the reaction was established by conversion of the enones **1b–d** into the rearranged enones **2b–d** and the results are summarised in Table 1. The starting materials **1a–d** were obtained by a one-pot Claisen rearrangement of the corresponding cinnamyl alcohols **3a–d** and 2-methoxypropene in the presence of a catalytic amount of propionic acid. The salient features are as follows. The presence of a catalytic amount of propionic acid accelerated this conversion, as the same reaction under identical conditions in the absence of propionic acid furnished less than 5% of **2a**. On the other hand, an increased amount of propionic acid resulted in a considerable amount of decomposition products. Ozonolysis of the enone **2b** furnished the known[4]† 2-methyl-1-phenylpentane-1,4-dione **6** confirming the structures of the rearranged products. The formation of the enone **2c** containing a methyl group on the olefin established, unambiguously, the proposed mechanism. The high ratios of **2c,d** to **1c,d** suggests the influence of the product stability on this conversion. The cinnamyl alcohols **3b–d** analogous to **3a**, when treated with 2-methoxypropene and propionic acid (catalytic) at 220–250 °C directly generated the same mixtures of the enones **2b–d** and **1b–d**.

This reaction has been extended to the synthesis of β-cuparenone **7**, a bicyclic sesquiterpene containing two

Table 1[a]

Entry	Starting enone **1**	Rearranged enone **2**	Yield (%)	Ratio **2** : **1**
a	**1a**	**2a**	68	67 : 33
b	 **1b**	 **2b**	66	67 : 33
c	 **1c**	 **2c**	66	90 : 10
d	 **1d**	 **2d**	75[b]	95 : 5

[a] All the reactions were carried out in toluene in a sealed tube at 230–250 °C under nitrogen atmosphere in the presence of propionic acid (5–10 μl) for 48 h. All the compounds gave spectral data (IR, ^1H and ^{13}C NMR, mass and high resolution mass) in good agreement with the structures assigned. [b] The same result was obtained even at 200–210 °C.

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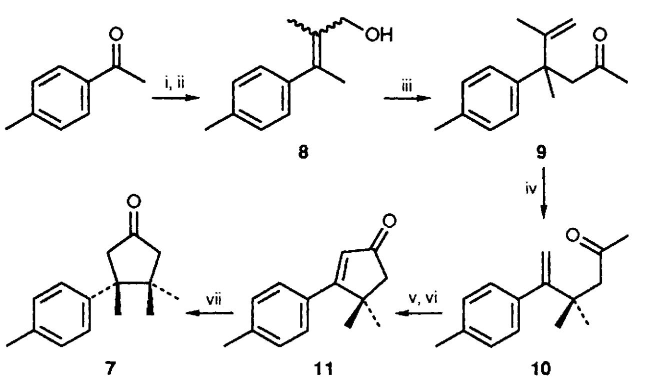
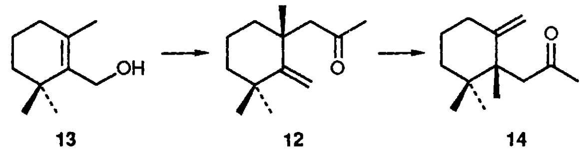
† Compounds **12** and **14** were separated by silica gel column chromatography. Compounds **11** and **2b** were purified by column chromatography after carrying out the ozonolysis. Compounds **2c**, **2d** and **11** were purified by crystallisation of the corresponding 2,4-DNP (2,4-dinitrophenylhydrazone) derivatives.

Compounds **6** and **11** exhibited spectral data identical to that reported in the literature.[4,9] *Spectral data* for **9**: IR (neat): ν_{max}/cm^{-1} 1710, 1641, 1515, 1377, 1359, 894, 816. δ_H (90 MHz, $CDCl_3$), 7.12 (4H, s), 4.95 (2H, s, $=CH_2$), 3.05 and 2.8 (2H, AB q, *J* 13 Hz, $COCH_2$), 2.32 (3H, s, $Ar–CH_3$), 1.82 (3H, s, $COCH_3$), 1.55 (6H, s, 2 × Me). δ_C (67.5 MHz, $CDCl_3$), 208.5 (C=O), 151.6 ($C{=}CH_2$), 143.4, 136.4, 129.6 (2C), 127.0 (2C), 111.1 ($C{=}CH_2$), 53.8 ($COCH_2$), 46.7 (C-4), 32.5 ($COCH_3$), 25.0, 21.4, 20.7. 2,4-DNP derivative m.p. 152–153 °C, satisfactory C, H and N analyses were obtained. For **10**: IR (neat): ν_{max}/cm^{-1} 1719, 1608, 1515, 1359, 900, 822. δ_H (90 MHz, $CDCl_3$), 7.05 (4H, m), 5.16 (1H, d, *J* 1.5 Hz), 4.85 (1H, d, *J* 1.5 Hz), 2.5 (2H, s, $COCH_2$), 2.34 (3H, s, $Ar–CH_3$), 2.05 (3H, s, $COCH_3$), 1.24 (6H, s, 2 × Me). δ_C (22.5 MHz, $CDCl_3$), 207.2 (s, C=O), 157.1 (s, $C{=}CH_2$), 139.9 (s), 136.0 (s), 129.0 (2C, d), 128.0 (2C, d), 113.0 (t, $C{=}CH_2$), 53.5 (t, $COCH_2$), 38.5 (s, C-4), 32.0 (q, $COCH_3$), 28.0 (2C, q, 2 × CH_3), 20.9 (q, $Ar–CH_3$). 2,4-DNP derivative m.p. 138–139 °C, satisfactory C, H and N analyses were obtained. For **14**: IR (neat): ν_{max}/cm^{-1} 1704, 1638, 1452, 1392, 1356, 1299, 1233, 1182, 1158, 897. δ_H (200 MHz, $CDCl_3$), 4.9 (1H, s), 4.65 (1H, s), 3.03 and 2.31 (2H, AB q, *J* 12.5 Hz, $COCH_2$), 2.2 (2H, m), 2.09 (3H, s, $COCH_3$), 1.0–1.8 (4H, m), 1.11 (3H, s), 0.89 (3H, s), 0.86 (3H, s). δ_C (22.5 MHz, $CDCl_3$), 208.0 (s, C=O), 150.7 (s, $C{=}CH_2$), 110.0 (t, $C{=}CH_2$), 47.3 (t, $COCH_2$), 44.9 (s), 37.4 (s), 36.5 (t), 32.9 (t), 31.5 (q, $COCH_3$), 24.4 (q), 23.1 (q), 22.9 (t), 17.5 (q). Mass; *m/z* 194 (M, 3%), 136 (60), 121 (36), 109 (70), 95 (70). HRMS: *m/z* Calc. for $C_{13}H_{22}O$, 194.1671; found, 194.1686.



Scheme 2 *Reagents and conditions*: i, NaH, $(EtO)_2P(O)CH(Me)CO_2Et$, THF, reflux, 14 h, 62%; ii, LAH, Et_2O, −70 °C, 2 h, 89%; iii, $CH_2{=}C(Me)OMe$, $EtCO_2H$, PhMe, 180 °C, 48 h, 62%; iv, PhMe, $EtCO_2H$, 230–250 °C, 48 h, 77%, 3 : 1 ratio of **10** and **9**; v, (a) O_3–O_2, CH_2Cl_2–MeOH, −50 °C; (b) PPh_3, −50 °C–room temp., 14 h, 62%; vi, MeOH, NaOH, reflux, 2 h, 81%; vii, see ref. 7



contiguous quaternary carbons isolated from *Thuja orientalis* (Muyur pankhi),[5] as depicted in Scheme 2. Thus, Wittig–Horner–Emmons reaction of *p*-methylacetophenone with triethyl α-phosphonopropionate using NaH as base in refluxing tetrahydrofuran (THF), followed by reduction of the resultant ester with $LiAlH_4$ generated the requisite cinnamyl alcohol **8**.[6] Claisen rearrangement of the cinnamyl alcohol **8** with 2-methoxypropene and propionic acid generated the enone **9**. Propionic acid-catalysed thermal rearrangement of the enone **9** at 230–250 °C for 48 h furnished, in 77% yield, a 75 : 25 mixture of the rearranged enone **10** and the starting enone **9**.† Ozonolysis of the enone **10** followed by base-catalysed cyclisation of the resultant diketone produced the cyclopentenone **11**,† an immediate precursor[7] to β-cuparenone **7**.

Finally, to test the feasibility of this rearrangement in other systems, thermolysis of the enone **12**, the Claisen rearrangement product of cyclogeraniol **13**,[8] was investigated. Thermal activation (250 °C) of the enone **12** in toluene in the presence of propionic acid (catalytic) furnished a 1 : 1 mixture of the starting enone **12** and the rearranged enone **14** in 75% yield.†

In conclusion, a novel rearrangement of γ,δ-unsaturated ketones to isomeric enones *via* an intramolecular ene reaction of the enol tautomer followed by a retro-ene reaction have been achieved. Direct formation of the rearranged enones from the allyl alcohols points to its synthetic utility.

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