An efficient microwave technique for \textit{exo-} to \textit{endo-} double bond migration in natural products

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Received 11 May 2009; accepted (revised) 8 February 2011

A few sesquiterpene lactones and monoterpenes when subjected to microwave irradiation on solid surface undergo facile carbon-carbon double bond migration from \textit{exo-} to \textit{endo-} position.

\textbf{Keywords:} Microwave, isomerization, sesquiterpene lactones, monoterpenes, natural products, pyrazolines

The interesting biological properties of sesquiterpene lactones and the possibility that they could represent a lead in the search for new chemicals of pharmaceutical and agrochemical interest has stimulated many research groups to develop methods for derivatization of the most promising targets of this group of compounds. On the basis of the plethora of the reports on sesquiterpene lactones bioactivity, it was of interest to obtain other biologically active derivatives of sesquiterpene lactones. Double bond shift is one of the major modifications to enhance the bioactivity of sesquiterpene lactones. In addition to this, industrial processes related to petrochemical oil-refining and selective olefin isomerization under mild conditions are of immediate interest to chemists. Boron trifluoride/etherate and iodine in dry benzene have been reported to bring about carbon-carbon double bond migrations in eremanthine and dehydrocostus lactone. The carbon-carbon double bond migrations using catalytic amounts of palladium chloride and triethylsilane have also been observed. Recently, singlet oxygen induced double bond migration has been reported during sulfide photooxidation. Selective transformation of some of the sesquiterpene lactones can also provide an entry to the partial synthesis of less abundant naturally occurring lactones. In this communication it is wished to report the carbon-carbon double bond migration from \textit{exo-} to \textit{endo-} position under microwave irradiation in natural products.

\textbf{Results and Discussion}

Microwave irradiation has been used in a wide variety of reactions on solid supports. The microwave assisted reactions offer considerable advantages over the conventional methods because of rapid heating and substantial rate enhancement of the reaction. Moreover, the reactions have proved to be cleaner concomitant with improvement in yield and selectivity. During the microwave induced decomposition of pyrazoline \textit{b} of isoalantolactone \textit{a}, it was observed that in addition to the desired compounds \textit{2a,b} (Ref. 10), two new compounds \textit{2c,d} were also isolated with increased time of irradiation.

| Chart 1 | Surprisingly, these two new compounds showed $^1$H and $^{13}$C NMR signals identical to \textit{13-}alkyl and \textit{11-}spirocyclopropyl derivative \textit{2a,b} except for the appearance of allylic methyl rather than exomethylene group thereby suggesting the occurrence of migration of the \textit{exo-} double bond into the ring. $^1$H NMR spectrum of the product \textit{2c} formed during this reaction displayed signal for vinylcyclic proton at $\delta$ 1.80 and a multiplet at $\delta$ 5.35 indicating that the isomerization occurred at $\Delta$4,15 position to $\Delta$3,4. This observation was also supported by the $^{13}$C NMR spectrum which showed an additional quartet at $\delta$ 21.5 and the absence of a triplet at $\delta$ 107.6. Similar spectral data was exhibited by the product \textit{2d}. This was a new observation of migration of the \textit{exo} double bond to the \textit{endo} position in microwave assisted reaction. Prompted by this observation, the same reaction was attempted on isoalantolactone \textit{a}, which was adsorbed on silica gel followed by microwave irradiation for 9 min 30 sec. After the usual work-up (see experimental section) a compound was obtained and identified by its spectral data as \textit{3}. $^1$H and $^{13}$C NMR spectrum of \textit{3} showed all the signals similar to those exhibited by isoalantolactone \textit{a} except for the absence of signal of exomethylene at $\Delta$4,15 rather than that of $\Delta$11,13. The establishment of the occurrence of double bond migration from $\Delta$4,15 to $\Delta$3,4 position was done on the basis of chemical shift difference of exomethylene protons of $\Delta$4,15 and $\Delta$11,13 in the original compound \textit{a}. The chemical shift difference of exomethylene protons of compound \textit{a} for $\Delta$4,15 and $\Delta$11,13 is $\delta$ 0.05 and $\delta$ 0.67, respectively, whereas in isomerised compound \textit{3}, the chemical shift difference...
is δ 0.67 attributable to Δ₁₁,₁₃ double bond and hence the isomerization at Δ₄,₁₅. A further support for this structure was achieved by comparing its spectral data with that obtained by conventional method. To further corroborate the occurrence of such type of reaction, dehydrocostus lactone was subjected to similar reaction conditions which gave the desired isomerized product. Interestingly, this compound has already been reported to be formed when is refluxed with iodine in dry benzene, though not in very good yield and accompanied by charring. An attempt to cause a similar double bond migration at C-10 position in failed due to polymerization of the starting material on further increasing the time of irradiation, which can fortuitously be put forth as the selectivity of the microwave mediated reaction. Based on these observations, it may be suggested that for a five membered ring in a guaianolide skeleton, sp³ hybridization for C-5 provides greater stability rather than sp² hybridization that would lead to increased strain in the molecule.

With the successful achievement of double bond migration under microwave irradiation for 1-3, several other sesquiterpenolides and a few monoterpenes were subjected to similar reactions (Table I). Interestingly, during the double bond isomerization in limonene under parallel conditions the major product obtained was 8, with irradiation time being 8 min. This could be explained by the fact that compound 8 might have been formed by the intermediacy of 7. In order to prove this, the same reaction was carried out for lower time intervals. The formation of 7 and 8 in the ratio 1:2 and sole product 8 after 5 min and 8 min of irradiation, respectively, proved the above conjecture. All the compounds were characterized on the basis of their spectral data (Table II).

**Experimental Section**

Melting points reported are uncorrected. The IR spectra were recorded in CHCl₃ solution on a Perkin Elmer model RX-1 FT-IR spectrometer and ¹H NMR spectra in CDCl₃ on Bruker AC 300 F (300 MHz) NMR spectrometer (chemical shifts in δ, ppm) with TMS as internal standard. All the chromatographic separations were performed over silica gel. Microwave induced reactions were carried out in a Kenstar M09706 domestic oven.

**Extraction of starting compounds:** The oil was obtained from the powdered roots of costus (Saussurea lappa) by Soxhlet extraction method in hexane followed by refrigeration and column chromatography of the solidified material to afford pure dehydrocostus lactone which was identified by comparison of its melting point and IR and ¹H NMR spectra with that of an authentic sample. Alantolides were obtained from the powdered roots of Inula racemosa by similar extraction procedures. The pyrazolines of isoalantolactone 1 was prepared by usual reaction with excess of diazoethane.

**Isomerization of 1 into 3 under microwave irradiation:** In a typical procedure, isoalantolactone (1.0 g) in dichloromethane (10 mL) was mixed thoroughly with silica gel (60-120 mesh) in a 100 mL
Table 1 — Comparison of reaction times in some double bond migration reactions by microwave and conventional methods

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Product</th>
<th>Reaction Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Reactant 1" /></td>
<td><img src="image2" alt="Product 1" /></td>
<td>9 min 30 sec</td>
<td>90</td>
</tr>
<tr>
<td><img src="image3" alt="Reactant 2" /></td>
<td><img src="image4" alt="Product 2" /></td>
<td>6 min 40 sec</td>
<td>85</td>
</tr>
<tr>
<td><img src="image5" alt="Reactant 3" /></td>
<td><img src="image6" alt="Product 3" /></td>
<td>5 min 80</td>
<td></td>
</tr>
<tr>
<td><img src="image7" alt="Reactant 4" /></td>
<td><img src="image8" alt="Product 4" /></td>
<td>8 min 75</td>
<td></td>
</tr>
<tr>
<td><img src="image9" alt="Reactant 5" /></td>
<td><img src="image10" alt="Product 5" /></td>
<td>5 min 30 sec</td>
<td>85</td>
</tr>
</tbody>
</table>
beaker and the solvent was removed under reduced pressure. The silica gel with adsorbed compound was then irradiated in a domestic microwave oven at an output of 640 W for 9 min 30 sec following a gap of 2 minutes between consecutive irradiations of 1 min each. After cooling to RT, the silica gel was eluted with dichloromethane (20 mL). The solvent was removed in vacuo to afford the corresponding isomerized product 3 (0.9 g).

Conclusion
In conclusion, it has been demonstrated that the efficiency and experimental simplicity of the present method for carbon-carbon double bond migration under microwave irradiation provide appreciable advantages in terms of rapid and regioselective route to derivatization of natural products as compared to methods previously employed for the purpose. Also, the absence of solvent in these reactions is beneficial from an environmental point of view.

Acknowledgement
The authors thank the Punjab Government for financial support under the project “Chemistry and potential of some natural products and synthetic heterocyclics as agrochemicals”.

References

Table II — Spectral characterization data of the isomerized products

<table>
<thead>
<tr>
<th>Compd</th>
<th>δ (CDCl3)</th>
<th>δ (CDCl3)</th>
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<tbody>
<tr>
<td>2c</td>
<td>5.35 (1H, m), 2.10 (1H, m), 2.69 (1H, m), 3.93 (1H, m), 1.09 (3H, s), 1.80 (3H, bs), 1.95 (2H, m), 5.91 (1H, t) and 1.12 (3H, t)</td>
<td>37.5 (C1-t, 22.8 (C2-t), 121.5 (C3-d), 134.7 (C4-s), 45.2 (C5-d), 26.3 (C6-t), 44.1 (C7-d), 77.5 (C8-d), 41.4 (C9-t), 31.8 (C10-s), 129.5 (C11-s), 171.6 (C12-s), 142.0 (C13-d), 16.3 (C14-t), 21.5 (C15-q), 22.6 (C16-t) and 14.3 (C17-q)</td>
</tr>
<tr>
<td>2d</td>
<td>5.32 (1H, d), 2.16 (1H, m), 2.64 (1H, m), 3.90 (1H, m), 1.05 (3H, s), 1.73 (3H, bs), 1.01 (1H, m), 0.65-0.37 (2H, m) and 0.95 (3H, d)</td>
<td>37.8 (C1-t), 22.2 (C2-t), 122.5 (C3-d), 135.6 (C4-s), 46.2 (C5-d), 26.3 (C6-t), 51.9 (C7-d), 78.5 (C8-d), 42.4 (C9-t), 31.5 (C10-s), 30.5 (C11-s), 170.6 (C12-s), 32.6 (C13-t), 17.9 (C14-t), 22.3 (C15-q), 15.6 (C16-d) and 21.6 (C17-q)</td>
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<td>3</td>
<td>6.22 (1H, d), 5.55 (1H, d), 5.30 (1H, m), 1.93 (3H, bs), 4.15 (1H, t) and 1.04 (3H, s)</td>
<td>37.3 (C1-t), 22.8 (C2-t), 122.04 (C3-s), 134.7 (C4-s), 44.6 (C5-d), 26.9 (C6-t), 40.5 (C7-d), 76.5 (C8-d), 40.4 (C9-t), 31.3 (C10-s), 142.5 (C11-s), 169.3 (C12-s), 120.4 (C13-t), 18.5 (C14-t) and 21.5 (C15-q)</td>
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<td>5</td>
<td>1.10 (3H, d), 5.35 (1H, t), 2.65 (1H, m), 4.92 and 5.10 (1H each, bs) and 5.45 and 6.12 (1H each, bs)</td>
<td>46.1 (C1-d), 32.8(C2-t), 125.3 (C3-s), 141.8 (C4-t), 55.3 (C5-t), 85.1 (C6-t), 46.0 (C7-t), 30.1 (C8-t), 35.4 (C9-t), 139.3 (C10-t), 137.8 (C11-t), 170.5 (C12-t), 118.0 (C13-t), 107.5 (C14-t) and 15.8 (C15-t)</td>
</tr>
<tr>
<td>7</td>
<td>2.65 (2H, m), 5.25 (1H, m), 1.80 (3H, s), 1.85 (3H, s) and 1.72 (3H, s)</td>
<td>31.2 (C1-t), 120.1 (C2-d), 134.4 (C3-s), 31.5 (C4-t), 26.0 (C5-t), 127.2 (C6-s), 121.1 (C7-t), 19.5 (C8-q), 18.8 (C9-q) and 22.0 (C10-q)</td>
</tr>
<tr>
<td>8</td>
<td>5.67 (1H, d), 5.65 (1H, d), 1.10 (6H, d) and 1.75 (3H, s)</td>
<td>116.1 (C1-d), 120.5 (C2-d), 134.1 (C3-s), 28.5 (C4-t), 25.7 (C5-t), 142.0 (C6-s), 33.8 (C7-d), 21.9 (C8-q), 20.2 (C9-q) and 24.5 (C10-q)</td>
</tr>
<tr>
<td>10</td>
<td>5.35 (1H, m), 0.94 (6H, d) and 1.70 (3H, s)</td>
<td>28.7 (C1-t), 120.5 (C2-d), 133.5 (C3-s), 30.5 (C4-t), 25.4 (C5-t), 40.1 (C6-d), 32.3 (C7-d), 31.1 (C8-q), 20.4 (C9-q) and 22.7 (C10-q)</td>
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