Monoterpenes are highly hydrophobic substances present in essential oils. They represent the most diverse class of natural products found in plants, with tens of thousands of reported structures. They are the substances derived from isoprene (2-methyl-1,3-butadiene) and originated by the attachment of two or more isoprene molecules. They cover a wide spectrum of biological effects actions of great importance in many different areas from food chemistry and chemical ecology to pharmacology and pharmaceutics.

The transformation of terpenes using efficient and selective methods is also of great interest for the preparation of new molecules of potential utility in the perfume or medicinal industry. A straightforward route for the modification of terpenes by cross-metathesis reactions. Direct transformations of several terpenes by cross-metathesis with methyl acrylate were presented in this paper. We performed these reactions in CHCl₃, xylene and glycerol solvents that were recently shown to be a green alternative to the undesirable dichloromethane or toluene in ruthenium catalyzed olefin metathesis transformations or under solvent free conditions.

INTRODUCTION

Monoterpenes are highly hydrophobic substances present in essential oils. They represent the most diverse class of natural products found in plants, with tens of thousands of reported structures. They are the substances derived from isoprene (2-methyl-1,3-butadiene) and originated by the attachment of two or more isoprene molecules. They cover a wide spectrum of biological effects actions of great importance in many different areas from food chemistry and chemical ecology to pharmacology and pharmaceutics.

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EXPERIMENTAL

All the reactions were conducted under an inert atmosphere of argon using standard Schlenck tube techniques. Solvents were dried by distillation prior to their use. CHCl₃, was dried over CaH₂, xylene over Na. All terpenes were purchased from Acros Organics and were used as they were received. Linalol (93 %), geraniol (95 %), citral (95 %, cis + 5 % trans mixture). Methyl acrylate was purchased from Acros Organics and stored under argon over 3 Å molecular sieves prior to their use. The key reactions were double checked. Elemental analyses were performed on Perkin-Elmer 2400 elemental analyzer and the values found were within ± 0.3 % of the theoretical values. ¹H NMR and ¹³C NMR spectra were carried on a Varian Gemini 200 (300 MHz) spectrometer using TMS as internal standard (δ = 0 ppm) and were recorded in CDCl₃, or DMSO-d₆, solutions spectra were recorded on a Perkin-Elmer 398 spectrophotometer.

General procedure for the cross-metathesis reactions with methyl acrylate: A dry and degassed Schlenck tube was loaded under argon with 100 mg of terpenoid (about 0.65 mmol), 8.0-8.3 mg of Hoveyda catalyst A (about 13.10⁻³ mmol, 2 mol %), 115-118 µL of methyl acrylate (about 1.3 mmol, 2 equiv.) and 2 mL of solvent. The reaction was stirred under the mentioned conditions. After solvent evaporation, the products were purified by column chromatography on silica gel using of EtOAc/petroleum ether mixtures.

Compound 2: Yield = 73 % (0.16 g), IR (KBr, ν max, cm⁻¹): 3295 (OH), 1656 (C=C), 1685 (C = O), ¹H NMR (300 MHz, CDCl₃, ppm): δ = 1.36 (s, 3H, CH₃), 1.68-1.76 (m, 2H, H₅), 2.13-2.30 (m, 2H, H₆), 3.74 (s, 3H, CO₂CH₃), 3.71 (s, 3H, CO₂CH₃), 5.81 (d, 1H, J = 15, 4 Hz, H₈), 6.05 (d, 1H, J = 15, 4 Hz, H₇), 6.94 (m, 2H, H₁, H₈). ¹³C NMR (50 MHz, CDCl₃, ppm): δ = 27.1 (CH₃), 28.5 (C₆), 40.2 (C₅), 51.9 (CO₂CH₃), 54.7 (CO₂CH₃), 170.9 (C=O).
52.1 (CO$_2$CH$_3$), 73 (C4), 119.3 (C8), 121.5 (C7), 149.2 (C2), 154 (C3), 167.4 (C1), 167.9 (C5). HRMS (ESI): [M+Na]$^+$ calculated for (C$_{10}$H$_{12}$O$_3$Na) = 205.1153. Measured: 205.1152. Anal. calcd for C$_{10}$H$_{14}$O$_3$: C, 65.77; H, 7.68. Found: C, 65.80; H, 7.60.

**Results and Discussion**

The transformation of several terpenes 1a-c was achieved by using three commercially available ruthenium based catalysts (Fig. 1).

Condensation of linalool with methyl acrylate under mild condensation in chloroform, xylene and glycerol afforded the corresponding terpenoids (2). Scheme-I describes the synthesis of compound 2 starting from linalool with methyl acrylate (MA). We used second generation Hoveyda catalyst A for screening the reaction conditions since it was previously proved to be the best catalyst in several transformations of compounds coming from biomass.$^{12-15}$

![Fig. 1. Terpenoids and ruthenium based catalysts tested in cross metathesis](image)

The compound 2 was characterized by using NMR and mass spectroscopic techniques and the proposed structure was supported the spectroscopic data. The $^1$H NMR spectra of compound 2 showed a singlet at $\delta$ 1.36 ppm for the CH$_3$ protons. A characteristic multiplet signal at $\delta$ 3.71 ppm was observed between H$_6$ and H$_7$.

The formation of the compound 2 was further confirmed by recording $^1$C NMR spectroscopy. The signal at $\delta$ 28.5 ppm corresponds to the C$_6$, C$_7$ carbon was observed at 40.2 ppm.
Other signals attributed respectively to the chemical shifts 51.9 ppm, 52.1 ppm and 73 ppm, corresponding to the carbons Cb, Ca and C4.

It is worth-considering that the cross-metathesis reaction was stereoselective producing only the E isomer. Decreasing the catalyst loading further to 1 mol % resulted in an extended polymerization side reactions requiring long and fastidious workup17. With contrast to the results obtained with methyl acrylate, under solvent free conditions catalysts B, C and D showed similar results as compared to A; i.e. full conversions and GC yields ranging between 90 and 98 %. The suggested mechanism for formation of compound 2 is given in Scheme-II.

The second double bond of linalool will engage in a second catalytic cycle identical to the first by reacting with methyl acrylate to form the final product 2 of cross metathesis between linalool and methyl acrylate.

Terpenoid (3) was synthesized via treatment of geraniol with methyl acrylate in glycerol, as depicted in Scheme-III. The reaction was performed under reflux either for 24h to yield compound 3 in good yield. Compound 3 was isolated by column chromatography and well characterized by spectral data.

Geraniol first reacted at low temperatures using 2 mol % of Hoveyda catalyst A and a two-fold excess of methyl acrylate. It is noteworthy that the reaction proceeded better in glycerol than in chloroform or xylene (Table-3, entries 1-3). This tendency was confirmed at 60 °C where glycerol again produced the best results.

It was proved here that the use of glycerol was not favourable for side reactions (Table-3, entry 4), This is the first time that such a solvent effect is observed with glycerol in an olefin metathesis transformation. This improvement led to a 10 % decrease of the transformation E factor18,19. Hence, using olefin cross-metathesis, the (E)-3 stereoisomer was stereoselectively prepared in 68 % yield thus showing an improvement with regard to the previously reported procedure where compound 3 was obtained in less than 60 % yield from a non-commercially available lactone20.

As we have observed in cross-metathesis of linalol, catalysts B, C and D were not as efficient as A. It was to be noted that the catalyst B was completely inactive for this transformation whereas catalysts C and D provided low to modest conversions of 32 and 70 %, respectively.

Then the commercially available citral was tested in cross-metathesis reactions with methyl acrylate (Scheme-IV). Condensation of citral with methylacrylate in different solvents: chloroform, xylene and glycerol. The reaction was undergoing smoothly to give terpenoid 4 in a good yield. Its

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Equiv. AM</th>
<th>Catal. (mol % A)</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
<th>Yield CPG (%)</th>
<th>Yield isolated (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHCl3</td>
<td>2</td>
<td>2</td>
<td>80</td>
<td>15</td>
<td>100</td>
<td>58</td>
<td>40</td>
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<tr>
<td>2</td>
<td>Xylene</td>
<td>2</td>
<td>2</td>
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<td>15</td>
<td>100</td>
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<td>42</td>
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<tr>
<td>3</td>
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<td>2</td>
<td>80</td>
<td>15</td>
<td>100</td>
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<td>44</td>
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<td>43</td>
</tr>
<tr>
<td>5</td>
<td>Glycerol</td>
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<tr>
<td>6</td>
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<td>70</td>
<td>3h</td>
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<tr>
<td>7</td>
<td>Glycerol</td>
<td>2</td>
<td>0.5</td>
<td>70</td>
<td>3h</td>
<td>100</td>
<td>70</td>
<td>35</td>
</tr>
</tbody>
</table>

aLinalol (100 mg, 0.65 mmol), methyl acrylate (117 mL, 1.3 mmol, 2 eq.), A (8.2 mg, 13.10-3 mmol, 2 mol %), solvent (2 mL). Conversions and GC yields determined using dodecane as an internal standard. b4 eq. of methyl acrylate. c10 eq. of methyl acrylate.

Interestingly, only the Zannan catalyst D featuring a structure close to A provided similar results whereas catalysts B and C showed poor efficiency (Table-2).

Table-2

<table>
<thead>
<tr>
<th>Conversion (%)</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>GC yield (%)</th>
</tr>
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<tbody>
<tr>
<td>90</td>
<td>B</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>98</td>
<td>C</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>92</td>
<td>D</td>
<td>3</td>
<td>85</td>
</tr>
</tbody>
</table>

Linalol (100 mg, 0.65 mmol), catalyst (0.5 mol %), methyl acrylate (117 mL, 1.3 mmol, 2 eq.), glycerol (2 mL), 80 °C, 3 h. Conversion and yields determined by gas chromatography using dodecane as an internal standard.
structure was identified by their IR, $^1$H, $^{13}$C NMR and mass spectra as well as by either their elemental analysis or high resolution exact mass measurement.

The IR spectrum of compound 4 indicated a characteristic adsorption bands at 1685 to 1604 cm$^{-1}$. These bands were attributed respectively to the C=O and C=C stretching vibrations. Its $^1$H NMR spectrum gave signals at $\delta$ 3.80, 5.70 and 9.70 ppm, characteristic respectively for CH$_3$, H$_3$ and CHO group.

The first tests with citral rapidly showed that the full conversion could be obtained and that the reaction proceeded with similar efficiency in xylene and glycerol (Table-4, entries 1-3). Therefore, the reaction was not selective and the required product 5 was the only product isolated but in a modest 44% yields (Table-4).
Attempts to isolate and identify the side products produced during the reaction failed but it must be mentioned that no conversion of citral with 2 mol % of A at 80 % C in xylene was observed.

**Reactivity of compound 4 towered hydrazines: Formation of heterocycles:** The reactivity of compound 4 towards hydrazine hydrate or phenyl hydrazine was studied and the reaction proceeded via an addition reaction on to the aldehyde group followed by intramolecular cyclization to produce the diazecin-3-ones (5) ring as in compound 5.

By reacting compound 4 with either hydrazine hydrate or phenyl hydrazine, respectively in the presence of glycerol at reflux diazecin-3-ones (5) was obtained in 65 % yield (Scheme-V).

The structures of compounds 5 were proved by spectral data and were consistent with the proposed structures.

The 1H NMR representative spectrum of compound 5a revealed the absence of the methoxy group protons and showed signal at 5.90 ppm for NH. The olefinic protons H4 and H5 resonate respectively at 7.66 and 5.82 ppm as doublets with J = 15.8 Hz, indicating an E stereochemistry.

The 13C NMR spectrum of compound 5a showed chemical shift signals at 167.5 ppm for C=O, 154.7 ppm for C=N, 143.5 (CH=CHCO) and 147.4 (CH=CHC=N).

**Conclusion**

In summary, we have prepared a series of new terpenoids by ruthenium catalyzed stereoselective cross-metathesis reactions. This catalytic transformation allowed the one step synthesis of terpenoids in higher yields than previously reported multistep procedures. Thus, not only were the product yields improved but also the waste production and energy consumption were decreased. Furthermore, these transformations were performed under environmental friendly conditions in glycerol. This type of transformation could certainly be extended to other terpenes or terpenoids and other cross metathesis partners. However, it will be necessary to identify and when possible to control the side reactions in order to improve further the performances of this process. We have also demonstrated the efficiency of olefin cross-metathesis for the synthesis of terpenoids, the control of the chemoselectivity of the cross-metathesis reaction is important and ring closing metathesis (RCM) reactions may also occur. Furthermore, the synthesis of some diazecin-3-ones is described via reaction of compound 4 with hydrazine hydrate or phenyl hydrazine in glycerol.

**ACKNOWLEDGEMENTS**

I would like to take this opportunity to thank Qassim University for its generosity to enable me to do this research activity and for confidence to help me achieve my goals.

**REFERENCES**


15. The reaction was also attempted under solvent-free conditions in 2ml of methyl acrylate. This procedure led to the formation of dimethyl fumarate and ethylene in sufficient amount to generate pressure in the reaction vessel. Since the results were not improved, this method was not further investigated.


19. Addition of 3 mol% of 2,6-Di-t-butyl-p-cresol as a Radical Scavenger was not sufficient to completely prevent the polymerisation of MMA.


23. Solvents, Catalyst and Unreacted Methyl Acrylate were considered as Wastes; Workup was not considered for the determination of E factor.

