Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Optimization of the Microwave-Assisted Ortho Ester Claisen Rearrangement: Application to Monoterpenols

Florence Mehl [a] , Isabelle Bombarda [a] , Carine Franklin [b] & Emile M. Gaydou [a]

[a] Paul Cezanne University, Faculty of Sciences and Technology of Saint-Jérôme, Molecular Science Institute of Marseille, Phytochemistry Group, Marseille, France

[b] Technological University Institute of Marseille, Chemistry Department, Marseille, France

Published online: 06 Jan 2010.

To cite this article: Florence Mehl , Isabelle Bombarda , Carine Franklin & Emile M. Gaydou (2010): Optimization of the Microwave-Assisted Ortho Ester Claisen Rearrangement: Application to Monoterpenols, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 40:3, 462-468

To link to this article: http://dx.doi.org/10.1080/00397910902985515

Synthetic Communications®, 40: 462–468, 2010

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910902985515

Taylor & Francis
Taylor & Francis Group

OPTIMIZATION OF THE MICROWAVE-ASSISTED ORTHO ESTER CLAISEN REARRANGEMENT: APPLICATION TO MONOTERPENOLS

Florence Mehl,[1] Isabelle Bombarda,[1] Carine Franklin,[2] and Emile M. Gaydou[1]

[1]*Paul Cezanne University, Faculty of Sciences and Technology of Saint-Jérôme, Molecular Science Institute of Marseille, Phytochemistry Group, Marseille, France*

[2]*Technological University Institute of Marseille, Chemistry Department, Marseille, France*

Two monoterpenols, perillyl alcohol and nerol, have been converted into their γ,δ-unsaturated ester derivatives following a modified process of microwave-assisted ortho ester Claisen rearrangement. The yields obtained (>90%) are better than those previously obtained. The optimized process needs less reaction time (5 min), smaller amount of reagent, and no solvent.

Keywords: Focused microwave; Johnson–Claisen; monoterpenol; ortho ester rearrangement

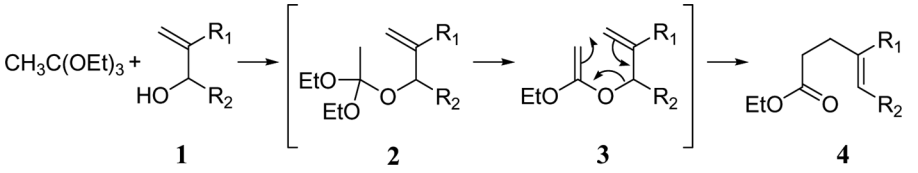
INTRODUCTION

In 1970, Johnson et al.[1] reported a variant of the original Claisen rearrangement. Instead of the conventional method,[2] generating a γ,δ-unsaturated aldehyde from allyl alcohols via the corresponding allyl vinyl ethers, Johnson and coworkers developed a one-pot procedure for generating γ,δ-unsaturated esters from allyl alcohols. In this method, heating an allyl alcohol **1** in an excess of triethyl orthoacetate (TEOA) in the presence of a trace amount of a weak acid furnishes the corresponding γ,δ-unsaturated esters **4**; this is now commonly referred as the ortho ester Claisen rearrangement (Scheme 1). This is a very useful reaction in organic synthesis to create a quaternary center in a one-pot reaction.

The use of microwave heating is attractive in organic synthesis.[3] Microwave irradiation has been shown not only to reduce reaction times but to provide better yields of the desired products than conventional heating methods.[4–7] The microwave heating technique[8–10] was used to carry out the ortho ester Claisen rearrangement. In 1995, Srikrishna et al.[8] described the application of the microwave heating

Received February 2, 2009.

Address correspondence to Isabelle Bombarda, Université Paul Cézanne, Faculté des Sciences et Techniques de Saint-Jérôme, UMR CNRS 6263, Institut des Sciences Moléculaires de Marseille, AD2EM, LSCC, Groupe Phytochimie, Boîte 461, Avenue Escadrille Normandie Niémen, F-13397 Marseille Cedex 20, France. E-mail: isabelle.bombarda@univ-cezanne.fr



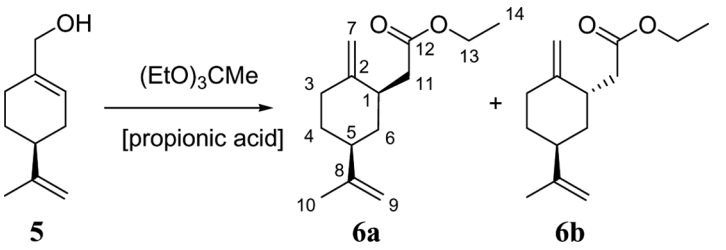
Scheme 1. Mechanism of the ortho ester Claisen rearrangement.

technique for rapid generation of γ,δ-unsaturated esters by acceleration of the ortho ester Claisen rearrangement. To carry out this rearrangement using microwave heating, a domestic microwave oven was employed. They experimented with different conditions [no solvent, methanol, chloroforme, hexane, dimethylformamide (DMF), in sealed tubes or in open vessels] and chose DMF as the best solvent because of its high dielectric constant and boiling point, and therefore reactions were carried out in open vessels.

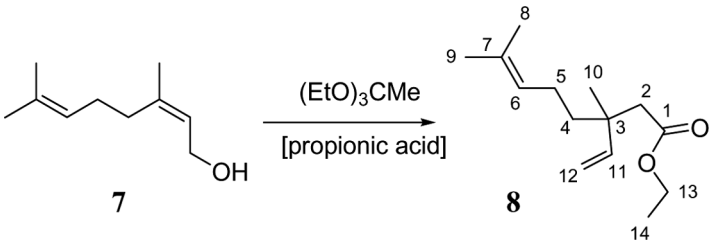
In this work, the ortho ester Claisen rearrangement was carried out in sealed tubes, without solvent, in a high-powered, focused microwave oven and with magnetic stirring. In the case of our reaction, the microwave increased reaction rates with thermal effect.[11] In fact, using microwave technology, products were heated directly instead of by convection and conduction, and we could work at a controlled temperature (190°C). A Biotage focused microwave with its powerful 400-W magnetron delivers precise heating control (measured by infrared, IR). Heating at this temperature was not possible with an oil bath because the temperature was limited by the boiling point of the reagent (138°C). We have screened microwave irradiation conditions (temperature and time), the molar ratio of terpenol/TEOA, and the role of solvent to optimize the process.

RESULTS AND DISCUSSION

The microwave-assisted ortho ester Claisen rearrangement was investigated with two monoterpenols: perillyl alcohol **5** and nerol **7**. The corresponding γ,δ-unsaturated esters **6** and **8** (Schemes 2 and 3) have already been obtained from these two monoterpenols under classical conditions (heating 8 h at 140°C with 7 eq of TEOA), and only ester **8** was synthesized under microwave irradiation conditions.



Scheme 2. Synthesis of γ,δ-unsaturated esters **6** from perillyl alcohol **5**.



Scheme 3. Synthesis of γ,δ-unsaturated esters **8** from nerol **7**.

Under classical conditions, esters **6** and **8** (140°C, 8 h, 7 eq) were obtained with yields similar to those obtained previously,[12,13] 84% (81% in literature) and 42% (67% after saponification in literature), as shown in Tables 1 and 2 (entries **a** and **a′**).

When nerol **7** was heated in a focused microwave oven at 190°C for 15 min in dry DMF (entry **b′**, Table 2), as described in the literature,[8] ester **8** was obtained with a yield similar to that previously given.[8] This microwave-assisted synthesis increased the yield of **8** from 42% up to 82% (entries **a′** and **b′**).

The reaction can give better yield without the use of solvent. In fact, the ester **6** was obtained from perillyl alcohol **5** with 95% yield (entry **b**) using the same method given for ester **8** in entry **b′** but without solvent. TEOA possess a dielectric constant, so it absorbs microwave energy, which is converted into warmth. Our process does not need any solvent, in contrast to that of Srikrishna et al.[8]

As shown in entries **b**, **c**, and **d**, the best amount of TEOA was found to be 14 eq. This result was confirmed with nerol because we obtained 87% yield for **8** using 14 eq of TEOA and 82% using 27 eq.

Three reaction times were tested with 7 eq of TEOA, and the best result (75%) was obtained after 5 min for **6** (entries **d**, **e**, and **f**). This optimized time was confirmed for **8** because we obtained a better yield in 5 min (93%) than in 15 min (87%, entries **c′** and **d′**).

Table 1. Johnson–Claisen rearrangement from perillyl alcohol **5** using either classical or microwave heating

Entry	Temperature (°C)	Time (min)	**5**:$(EtO)_3CMe$[a]	Product	Yield (%)
a	140[b]	480	1:7	**6**	84
b	190[c]	15	1:27	**6**	95
c	190[c]	15	1:14	**6**	95
d	190[c]	15	1:7	**6**	73
e	190[c]	10	1:7	**6**	70
f	190[c]	5	1:7	**6**	75
g	190[c]	5	1:14	**6**	99

[a]Molecular ratio.
[b]In oil bath.
[c]Under microwaves.

Table 2. Johnson–Claisen rearrangement from nerol **7** using either classical or microwave heating

Entry	Temperature (°C)	Time (min)	**7**:$(EtO)_3CMe$[a]	Product	Yield (%)
a′	140[b]	480	1:7	**8**	42
b′	190[c]	15	1:27	**8**	82
c′	190[d]	15	1:14	**8**	87
d′	190[d]	5	1:14	**8**	93

[a]Molecular ratio.
[b]In oil bath.
[c]In DMF.
[d]Under microwaves.

With this study, we proved that the best conditions for the Claisen ortho ester rearrangement is to heat the mixture of allyllic alcohol with 14 eq of TEOA in a sealed tube for 5 min at 190°C in a microwave oven. We obtained excellent yields for **6** and **8** (99% and 93% respectively, entries **g** and **d′**). Unlike Srikrishna et al., we do not use any solvent other than the reagent, the reaction time is shorter (5 min instead of 12), and the yield of **8** obtained from nerol is better (93% versus 87% for Srikrishna et al.).[8] Furthermore, the microwave oven used is high powered and focused, and all reaction conditions (such as temperature, pressure, stirring) are controllable, so the reaction carried out in this oven is repeatable.

CONCLUSION

We have optimized the ortho ester rearrangement process using focused microwave oven heating. The significant features of this method include operational simplicity, repeatability, high yields, and short reaction time. Unlike other methods, no solvent is employed. Less energy is needed.

EXPERIMENTAL

The NMR spectra were recorded on a Bruker Avance DPX-300 (300-MHz) instrument and a Bruker Avance DRX-500 (500-MHz) instrument. Triethyl orthoacetate and perillyl alcohol were purchased from Sigma-Aldrich and nerol was obtained from Fluka in high quality, and they were used without any further purification.

Typical Procedure

A stirred mixture of allylic alcohol (0.231 g, 1.50 mmol), TEOA (4 mL, 22 mmol), and a catalytic amount of propionic acid (6 μL, 0.08 mmol) was heated in a sealed tube at 190°C in a microwave oven (Biotage, Initiator) for 5 min at an inside pressure of the reaction vessel of less than 7 bar. The excess of TEOA was hydrolyzed with HCl 1 N, and then the mixture was extracted with diethyl ether. The combined extracts were washed with brine, dried over $MgSO_4$, and evaporated

under reduced pressure. The yellow oil obtained was purified by column chromatography over silica gel using *n*-heptane/ethyl acetate (8:2, v/v) as eluent to give a mixture of esters as oil.

Ethyl 2-((1R,5S)-2-Methylene-5-(prop-1-en-2-yl)cyclohexyl)acetate (6a) and Ethyl 2-((1S,5S)-2-Methylene-5-(prop-1-en-2-yl)cyclohexyl)-acetate (6b)

Esters **6a** and **6b** (80/20, GC relative percentage) were obtained quantitatively as a colorless oil (0.347 g, 1.58 mmol) from (7*S*)-(–)-perillyl alcohol **5** (0.240 g, 1.58 mmol).

Ethyl 2-((1R,5S)-2-Methylene-5-(prop-1-en-2-yl)cyclohexyl)acetate (6a)

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, $J = 7.2$ Hz, 3 H), 1.61 (ddd, $J = 13.0$ Hz, $J = 11.9$ Hz, $J = 5.0$ Hz, 1 H), 1.72 (s, 3 H), 1.72 (m, 1 H), 1.84 (m, 1 H), 2.25 (m, 3 H), 2.47 (dd, $J = 14.0$ Hz, $J = 7.6$ Hz, 1 H), 2.55 (dd, $J = 14.0$ Hz, $J = 8.2$ Hz, 1 H), 2.96 (m, 1 H), 4.13 (q, $J = 7.2$ Hz, 2 H), 4.69 (m, 1 H), 4.73 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.34 (C-14), 21.00 (C-10), 30.96 (C-3), 32.88 (C-4), 36.77

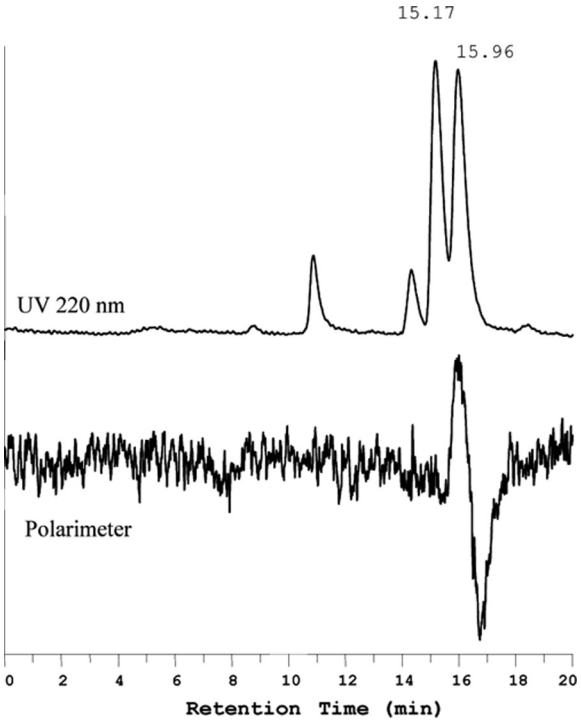


Figure 1. Chiral HPLC of compound **8** on Chiralcel OD-H (Chiralcel OD-H (250 × 4.6 mm) column, 0.5 mL/min *n*-hexane, detection: UV220 nm and polarimeter, 25°C).

(C-6), 39.19 (C-5), 39.72 (C-1), 38.26 (C-11), 60.29 (C-13), 108.83 (C-7), 109.09 (C-9), 149.33 (C-8), 149.64 (C-2), 172.60 (C-12).

Ethyl 2-((1S,5S)-2-Methylene-5-(prop-1-en-2-yl)cyclohexyl)acetate (6b)

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (q, $J = 12.3$ Hz, 1 H), 1.27 (m, 1 H), 1.28 (q, $J = 7.2$ Hz, 3 H), 1.72 (s, 3 H), 1.90 (m, 2 H), 2.16 (m, 1 H), 2.23 (m, 1 H), 2.25 (m 1 H), 2.28 (dd, $J = 15.0$ Hz, $J = 7.6$ Hz, 1 H), 2.41 (dt, $J = 13.2$ Hz, $J = 2.6$ Hz, 1 H), 2.66 (dd, $J = 15.0$ Hz, $J = 6.5$ Hz, 1 H), 4.13 (q, $J = 7.2$ Hz, 2 H), 4.54 (m, 1 H), 4.73 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.30 (C-14), 20.85 (C-10), 33.47 (C-4), 36.49 (C-3), 38.08 (C-11), 39.19 (C-1), 39.48 (C-6), 45.30 (C-5), 60.36 (C-13), 104.80 (C-7), 108.83 (C-9), 149.50 (C-8), 151.17 (C-2), 173.15 (C-12).

Ethyl-3,7-dimethyl-3-vinyloct-6-enoate (8)

Ester **8** was obtained without enantioselectivity as a light yellow oil with 83% isolated yield (1.113 g, 5 mmol) from nerol **7** (0.924 g, 6 mmol). The two enantiomers were obtained without selectivity [Chiral HPLC on Chiralcel OD-H (250 × 4.6 mm) column, 0.5 mL/min *n*-hexane, detection with UV220 nm and polarimeter, 25°C] (Fig. 1). $[\alpha]_D^{20} = 0$ (c = 0.16; CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 3 H), 1.17 (t, $J = 7.1$ Hz, 3 H), 1.32–1.37 (m, 2 H), 1.51 (s, 3 H), 1.60 (s, 3 H), 1.80–1.86 (m, 2 H), 2.24 (s, 2 H), 4.03 (q, $J = 7.1$ Hz, 2 H), 4.92 (dd, $J_{gem} = 1.1$ Hz, $J_{trans} = 17.5$ Hz, 1 H), 4.95 (dd, $J_{gem} = 1.1$ Hz, $J_{trans} = 17.5$ Hz, 1 H), 5.00 (m, 1 H), 5.75 (dd, $J_{cis} = 10.8$ Hz, $J_{trans} = 17.5$ Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.52 (C-14), 17.79 (C-10), 23.09 (C-5), 23.45 (C-8), 25.88 (C-9), 39.39 (C-3), 40.85 (C-4), 45.17 (C-2), 60.19 (C-13), 112.27 (C-12), 124.67 (C-6), 131.59 (C-7), 145.76 (C-11), 171.97 (C-1).

REFERENCES

1. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T. T.; Faulkner, D. J.; Petersen, M. R. A simple stereoselective version of the Claisen rearrangement leading to *trans*-trisubstituted olefinic bonds: Synthesis of squalene. *J. Am. Chem. Soc.* **1970**, *92*, 741–743.
2. (a) Claisen, L. Rearrangement of phenyl allyl ethers in C-allylphenols. *Chem. Ber.* **1912**, *45*, 3157–3166; (b) Ziegler, F. E. The thermal, aliphatic Claisen rearrangement. *Chem. Rev.* **1988**, *88*, 1423–1452.
3. Loupy, A. *Microwaves in Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, 2006.
4. Chemat-Djenni, Z.; Hamada, B.; Chemat, F. Atmospheric pressure microwave assisted heterogeneous catalytic reactions. *Molecules* **2007**, *12*, 1399–1409.
5. Hedidi, M.; Hamdi, S. M.; Mazari, T.; Boutemeur, B.; Rabia, C.; Chemat, F.; Hamdi, M. Microwave-assisted synthesis of calix[4]resorcinarenes. *Tetrahedron* **2006**, *62*, 5652–5655.
6. Roberts, B. A.; Strauss, C. R. Toward rapid, "green," predictable microwave-assisted synthesis. *Acc. Chem. Res.* **2005**, *38*, 653–661.
7. De la Hoz, A.; Diaz-Ortiz, A.; Moreno, A. Microwaves in organic synthesis: Thermal and non-thermal microwave effects. *Chem. Soc. Rev.* **2005**, *34*, 164–178.
8. Srikrishna, A.; Nagaraju, S.; Kondaiah, P. Application of microwave heating technique for rapid synthesis of γ,δ-unsaturated esters. *Tetrahedron* **1995**, *51*, 1809–1816.

9. Abramovitch, R. A. Applications of microwave energy in organic chemistry: A review. *Org. Prep. Proc. Int.* **1991**, *23*, 683–711.
10. Tymoshenko, D. O. Microwave-assisted Claisen and aza-Claisen rearrangements. *Mini-Rev. Org. Chem.* **2008**, *5*, 85–95.
11. Herrero, M. A.; Kremsner, J. M.; Kappe, C. O. Nonthermal microwave effects revisited: On the importance of internal temperature monitoring and agitation in microwave chemistry. *J. Org. Chem.* **2008**, *73*, 36–47.
12. Paruch, E.; Ciunik, Z.; Nawrot, J.; Wawrzenczyk, C. Lactones, 9: Synthesis of terpenoid lactones active insect antifeedants. *J. Agric. Food Chem.* **2000**, *48*, 4973–4977.
13. Günther, H. J.; Guntrum, E.; Jäger, V. Synthese von 4-Penten-4-oliden(γ-Methylen-α-butyrolactonen) über 4-Pentensäuren. *Lieb. Ann. Chem.* **1984**, 15–30.