Ruthenium-catalyzed estragole isomerization: high *trans*-selective formation of anethole†‡

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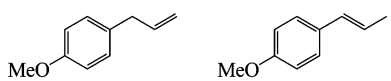
Complexes $[RuCl_2(\eta^6\text{-}C_6H_5OCH_2CH_2OH)(L)]$ (L = $P(OMe)_3$ (**1a**), $P(OEt)_3$ (**1b**), $P(O^iPr)_3$ (**1c**), $P(OPh)_3$ (**1d**), PPh_3 (**1e**)) have shown to be efficient catalysts for the isomerization of estragole into anethole, the best activities being obtained in polar solvents (water, methanol, ethanol). Interestingly, a complete selectivity toward *trans*-anethole could be reached under smooth conditions (80 °C) and in very short times (5–15 min). The catalytic experiments have been performed both under conventional and microwave heating, reaction rates being significantly enhanced under the latter conditions.

Introduction

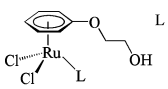
Trans-anethole (Fig. 1),[1] also known as *trans*-methylchavicol or *trans*-isoestragole, presents important applications in food and beverage industries[2] and in the formulation of oral hygiene products.[3] Furthermore, it is a valuable intermediate for the synthesis of pharmaceutical compounds[4] and perfumery chemicals.[5] *Trans*-anethole is a naturally-occurring product which has been traditionally extracted from anise or fennel oils, albeit with variable proportions of its *cis*-isomer as an impurity. However, the increasing industrial demand has made it necessary to develop alternative synthetic routes. From an academic point of view, several methodologies have been reported to access to anethole through different coupling processes,[6] nevertheless they are not financially viable. Actually, industrial process is based on the isomerization of estragole (Fig. 1) promoted by excess of KOH or NaOH.[7] A number of drawbacks are associated to this procedure: (i) the high temperature required (>200 °C), (ii) the poor conversion into anethole (*ca.* 60%) and (iii) the huge quantity of basic wastes generated. Another important aspect of this process is its stereoselectivity. Effectively, only *trans*-anethole is interesting for industry since the *cis*-isomer presents a higher toxicity and unpleasant odour and taste.[8] Accordingly, food regulatory instructions limit the proportion of *cis*-anethole to a maximum of 1%.[9] The current commercial process generates anethole with a *trans* : *cis* ratio of 82 : 18, therefore making necessary an additional separation step of the isomers.



Estragole *trans-Anethole*

Fig. 1 Structure of estragole and anethole.

Alternatively, isomerization of estragole into anethole can be promoted by metallic precursors;[10,11] nevertheless, most of them also conduce to a moderate selectivity in the *trans* isomer.[12] Recently, we have reported that arene-ruthenium(II) complexes $[RuCl_2(\eta^6\text{-}C_6H_5OCH_2CH_2OH)(L)]$ (**1a–e**, Fig. 2) efficiently isomerize allylic alcohols into saturated carbonyl compounds, through an initial C=C metal-catalyzed migration followed by a spontaneous tautomerization of the resulting enol.[13] Then, their capacity to promote C=C bond migration prompted us to evaluate their efficiency and selectivity in the transformation of estragole into anethole.[14]



L = $P(OMe)_3$ (**1a**), $S_{20°C}$ = 755 g.L^{-1}
$P(OEt)_3$ (**1b**), $S_{20°C}$ = 27.2 g.L^{-1}
$P(O^iPr)_3$ (**1c**), $S_{20°C}$ = 67.3 g.L^{-1}
$P(OPh)_3$ (**1d**), $S_{20°C}$ < 0.5 g.L^{-1}
PPh_3 (**1e**), $S_{20°C}$ < 0.5 g.L^{-1}

Fig. 2 Structure of complexes **1a–e** and their solubility in water at 20 °C ($S_{20°C}$).

Interestingly, these complexes are readily accessible in two-steps from commercially available starting materials and present a high solubility and stability in water, therefore allowing their use in environmental benign aqueous media.[13] Herein, we describe their application in the highly *trans*-selective formation of anethole from estragole. In this study, the efficiency of both conventional and microwave heating conditions has been explored.

Results and discussion

Catalytic isomerization of estragole into anethole under conventional heating

Firstly, the catalytic activity of complexes $[RuCl_2(\eta^6\text{-}C_6H_5OCH_2CH_2OH)(L)]$ (L = $P(OMe)_3$ (**1a**), $P(OEt)_3$ (**1b**), $P(O^iPr)_3$ (**1c**), $P(OPh)_3$ (**1d**), PPh_3 (**1e**)) in the isomerization of estragole has been checked in an aqueous medium. Experiments were performed at 80 °C using 4 mmol of substrate, 1 mol% of

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† Dedicated to Dr Bernard Demerseman on the occasion of his retirement.

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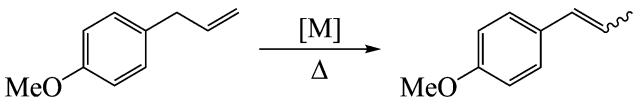
Table 1 Isomerization of estragole into anethole catalyzed by $[RuCl_2(\eta^6\text{-}C_6H_5OCH_2CH_2OH)(L)]$ (**1a–e**) in water.[a]

Entry	Catalyst [L]	Time/h	Yield (%)[b]	*trans* : *cis*[b]
1	**1a** $[P(OMe)_3]$	2	>99	92 : 8
2	**1b** $[P(OEt)_3]$	1.5	>99	95 : 5
3	**1c** $[P(O^iPr)_3]$	0.5	>99	90 : 10
4	**1d** $[P(OPh)_3]$	23	>99	96 : 4
5	**1e** $[PPh_3]$	4.5	>99	93 : 7
6[c]	**1c** $[P(O^iPr)_3]$	21	>99	91 : 9
7[d]	**1c** $[P(O^iPr)_3]$	0.5	98	91 : 9
8[e]	**1c** $[P(O^iPr)_3]$	0.5	84	81 : 19

[a] Unless otherwise indicated, reactions were carried out at 80 °C, using 4 mmol of estragole, 1 mol% of Ru and 1 mL of water. [b] GC determined. [c] At 35 °C. [d] With NaOH (1 equiv. per Ru). [e] With H_2SO_4 (1 equiv. per Ru).

Ru and 1 mL of water (Table 1 and Scheme 1), the reaction being monitored by GC analyses of aliquots.



Scheme 1 Catalytic isomerization of estragole into anethole.

For all the catalysts, complete conversion into anethole was reached, nevertheless the rate of the process was strongly dependent of the ligand L coordinated on the metal center. Thus, complexes containing an aliphatic phosphite (**1a–c**), *i.e.* the most soluble in water (see Fig. 2), gave rise to quantitative yields in anethole within 2 h (entries 1–3 in Table 1). The best results were obtained with $[RuCl_2(\eta^6\text{-}C_6H_5OCH_2CH_2OH)\{P(O^iPr)_3\}]$ (**1c**) which quantitatively converted estragole into anethole in only 30 min (entry 3).

In contrast, the presence of an aromatic ligand in the coordination sphere of ruthenium resulted in lower catalytic activities. In particular, the triphenylphosphite derivative (**1d**) needed 23 h to transform estragole into anethole (entry 4, Table 1).[15] In all the cases, good selectivity in the *trans* isomer was observed (90–96%), although the proportion never exceeded the desired value of 99%. In an attempt to improve the selectivity, the process has been carried out at lower temperature (35 °C) with the most active complex **1c** (entry 6, Table 1). Unfortunately, the *trans*-selectivity remained almost unchanged (91% *vs.* 90%), while the reaction time dramatically increased (21 h *vs.* 0.5 h). We next explored the influence of the pH medium onto the catalytic performances. Thus, reactions were performed in the presence of one equivalent per ruthenium of NaOH or H_2SO_4. The results obtained under basic conditions were similar to those observed in neutral water (entry 7 *vs.* entry 3, Table 1). In contrast, the addition of an acid was detrimental both to the yield and the selectivity (entry 8).

We also investigated how the process is affected by changing the catalyst loading. We observed that raising the quantity of ruthenium from 1 to 2 mol% did not modify the *trans* : *cis* ratio (entry 6 *vs.* entry 5, in Table 2). On the other hand, lower metal loadings (0.2 or 0.05 mol%) conduced to lower selectivities in the desired *trans*-isomer (entries 1–4 *vs.* 5).

The isomerization of estragole promoted by $[RuCl_2(\eta^6\text{-}C_6H_5OCH_2CH_2OH)\{P(OMe)_3\}]$ (**1a**) has also been tested in

Table 2 Influence of the ruthenium loading.[a]

Entry	mol% of catalyst	Time/h	Yield (%)[b]	*trans* : *cis*[b]
1	0.05	0.5	1	—[c]
2	0.05	22	76	83 : 17
3	0.2	0.5	88	83 : 17
4	0.2	2	>99	86 : 14
5	1	0.5	>99	90 : 10
6	2	0.5	>99	90 : 10

[a] Reactions carried out at 80 °C, using 4 mmol of estragole, the indicated loading of **1c** and 1 mL of water. [b] GC determined. [c] Not determined.

Table 3 Influence of the solvent.[a]

Entry	Solvent	Time/h	Yield (%)[b]	*trans* : *cis*[b]
1	hexane	20	>99	92 : 8
2	toluene	17	97	96 : 4
3	1,4-dioxane	2	>99	92 : 8
4	THF	1.5	>99	96 : 4
5	*tert*-butanol	1.25	>99	95 : 5
6	isopropanol	0.75	>99	95 : 5
7	ethanol	0.5	>99	99 : 1
8	methanol	0.25	>99	>99% *trans*[c]
9	acetonitrile	18	15	93 : 7
10	water	2	>99	92 : 8

[a] Reactions carried out at 80 °C, using 4 mmol of estragole, 1 mol% of **1a** and 1 mL of the indicated solvent. [b] GC determined. [c] *cis* isomer not detected.

different solvents (see Table 3). As a general trend, the rate of the process increased with the polarity of the solvent. Thus, in hexane or toluene, long reaction times, superior to 17 h, were necessary to reach significant conversions (entries 1–2, Table 3). In contrast, in polar solvents, and especially in alcohols, the isomerization proceeded rapidly.[16] Remarkably, complete conversion in only 15 min was observed when methanol was used as solvent (entry 8). Finally, although acetonitrile was one of the most polar solvent used, the conversion obtained in this medium was particularly low (15% after 18 h, entry 9). This is probably due to its capacity to coordinate on the active species, competing then with the substrate.

As far as selectivity is concerned, methanol and ethanol are revealed to be the solvents of choice. Effectively, under these conditions the proportion of *trans*-anethole obtained was equal or superior to 99% (entries 7 and 8 in Table 3). In particular, when the reaction was carried out in methanol no *cis* isomer was detected neither by GC analyses nor by ^1H and $^{13}C\{^1H\}$ NMR spectroscopy of the isolated product (see ESI‡), evidencing the complete stereoselectivity of the process.

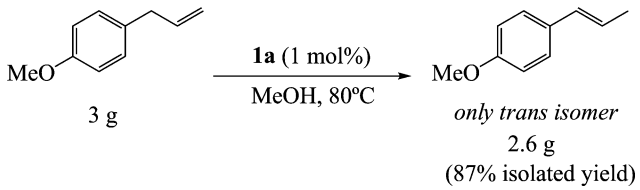
The catalytic studies in ethanol and methanol have been extended to the other aliphatic catalysts **1b** and **1c** (Table 4).[17] In all the cases, complete conversion was reached in short reaction times (≤1 h) and excellent *trans*-selectivities were observed (≥97%).

Interestingly, the isomerization of estragole can be easily scaled-up, affording multiple grams of isolated *trans*-anethole in a total stereoselective manner (Scheme 2, see details in the Experimental section).

Table 4 Isomerization of estragole catalyzed by [$RuCl_2(\eta^6$-$C_6H_5OCH_2CH_2OH)(L)$] (**1a–e**) in ethanol and methanol.[a]

Entry	Catalyst [L]	Time/h	Yield (%)[b]	*trans* : *cis*[b]
1[c]	**1a** [$P(OMe)_3$]	0.5	>99	99 : 1
2[c]	**1b** [$P(OEt)_3$]	0.5	>99	99 : 1
3[c]	**1c** [$P(O^iPr)_3$]	1	>99	97 : 3
4[d]	**1a** [$P(OMe)_3$]	0.25	>99	>99% *trans*[e]
5[d]	**1b** [$P(OEt)_3$]	0.25	>99	99 : 1
6[d]	**1c** [$P(O^iPr)_3$]	0.42	>99	98 : 2

[a] Reactions carried out at 80 °C, using 4 mmol of estragole, 1 mol% of Ru and 1 mL of solvent. [b] GC determined. [c] Ethanol used as solvent. [d] Methanol used as solvent. [e] *cis* isomer not detected.



Scheme 2 Stereoselective isomerization of estragole in preparative scale.

Catalytic isomerization of estragole into anethole under microwave heating

During the last decade, microwave-assisted organic synthesis has emerged as an important issue in green chemistry,[18,19] since the use of this heating technique significantly shortens reaction times, therefore minimizing the energy consumption during the process. Moreover, in many cases it also minimizes side reactions and improves the yield, selectivity and reproducibility of the process. Therefore, we explored the activity of catalysts **1a–e** in the isomerization of estragole under microwave heating (Table 5). The first experiments were carried out in water keeping the ruthenium loading (1 mol%), the substrate concentration (4 M) and the temperature (80 °C) as before (see details in the Experimental section). Under these conditions, reaction rates attained with all the catalysts were significantly higher than those obtained under conventional heating.[20] The most impressive enhancement was observed with complex **1e** which led to 97% yield of anethole after only 15 min (*vs* 21% yield under conventional heating). The best results in terms of yield and selectivity were reached with catalysts **1b** and **1c** which gave rise to complete conversion within 15 min and a *trans*-selectivity of 94-95% (entries 2–3, Table 5). As was observed under conventional heating, even better catalytic performances could be achieved in methanol. In particular, it is noteworthy that catalyst **1a** afforded a complete and fully-selective transformation of estragole into *trans*-anethole in only 5 min (entry 6).

Table 5 Isomerization of estragole under microwave heating.[a]

Entry	Catalyst	Solvent	Time	Yield (%)[b]	*trans* : *cis*[b]
1	**1a**	water	15 min	80	90 : 10
2	**1b**	water	15 min	>99	95 : 5
3	**1c**	water	15 min	>99	94 : 6
4	**1d**	water	15 min	15	80 : 20
5	**1e**	water	15 min	97	86 : 14
6	**1a**	MeOH	5 min	99	>99% *trans*[c]
7	**1b**	MeOH	5 min	98	99 : 1
8	**1c**	MeOH	5 min	80	98 : 2

[a] Reactions carried out under MW heating at the indicated temperature, using 4 mmol of estragole, 1 mol% of Ru and 1 mL of solvent. [b] GC determined. [c] *cis* isomer not detected.

Conclusions

In summary, the arene-ruthenium(II) complexes [$RuCl_2(\eta^6$-$C_6H_5OCH_2CH_2OH)(L)$] (L = $P(OMe)_3$ (**1a**), $P(OEt)_3$ (**1b**), $P(O^iPr)_3$ (**1c**), $P(OPh)_3$ (**1d**), PPh_3 (**1e**)), and especially the aliphatic ones, have shown to be effective catalysts to convert estragole into anethole. The best activity and selectivity toward *trans*-anethole were obtained in polar solvents (*i.e.* water, ethanol and methanol). In particular, in ethanol and methanol, it is possible to generate anethole with a contain in *trans*-isomer ≥99%, fulfilling therefore the criteria imposed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA).[9] Very short reaction times are required under conventional heating (*ca.* 15 min) and even shorter under microwave-irradiations (*ca.* 5 min). Thus, this process represents a rapid and highly selective access to *trans*-anethole compatible with renewable solvents such as water, EtOH or MeOH.[21]

Experimental

Solvents were dried by standard methods and distilled under nitrogen before use. All reagents were obtained from commercial suppliers with the exception of compounds [$RuCl_2(\eta^6$-$C_6H_5OCH_2CH_2OH)(L)$] (L = $P(OMe)_3$ (**1a**), $P(OEt)_3$ (**1b**), $P(O^iPr)_3$ (**1c**), $P(OPh)_3$ (**1d**), PPh_3 (**1e**)),[13] which were prepared following the method reported in the literature. NMR spectra were recorded on a Bruker DPX300 instrument at 300 MHz (^1H), 121.5 MHz (^{31}P) or 75.4 MHz (^{13}C) using $SiMe_4$ or 85% H_3PO_4 as standards. GC measurements were made on a Hewlett-Packard HP6890 equipment (Supelco Beta-Dex™ 120 column; 30 m length; 250 μm diameter).

Typical procedure for catalytic isomerization of estragole into anethole under conventional heating

Under a nitrogen atmosphere, the ruthenium catalyst precursor (0.04 mmol, 1 mol%), 1 mL of the indicated solvent and estragole (0.614 mL, 4 mmol) were introduced into a teflon-cap sealed tube. Then, the mixture was heated at 80 °C and, the yield and selectivity of the reaction were monitored by GC analyses of aliquots.

Typical procedure for catalytic isomerization of estragole into anethole under microwave heating

A pressure-resistant septum-sealed glass microwave reactor was charged under nitrogen atmosphere with estragole (0.614 mL, 4 mmol), the corresponding ruthenium catalyst precursor (0.04 mmol, 1 mol%), a magnetic stirring bar and 1 mL of distilled water or methanol. The vial was then placed inside the cavity of a CEM Discover® S-Class microwave synthesizer and power was held at 100 W until the desired temperature was reached (80 °C). Microwave power was automatically regulated for the remainder of the experiment to maintain the temperature

(monitored by a built-in infrared sensor). The internal pressure during the reaction ranged between 15 and 25 psi. After the time indicated (5 or 15 min), the vial was cooled and yield and selectivity were determined by GC analyses.

Isomerization of estragole into anethole under preparative conditions (conventional heating)

Under a nitrogen atmosphere, the precursor **1a** (0.081 g, 0.2 mmol, 1 mol%), 5 mL of distilled MeOH and 3.1 mL of estragole (20 mmol) were introduced into a teflon-cap sealed tube and heated at 80 °C for 20 min. After this time, GC analysis revealed a complete conversion and a *trans*-selectivity of 99%. After removal of the solvent under vacuum, flash chromatography of the residue using ethyl acetate as eluent afforded 2.6 g (17.5 mmol, 88%) of analytically pure *trans*-anethole.

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20 After 15 min under conventional heating the following yields and selectivity were obtained: 28%, *trans* : *cis* = 87 : 13 (**1a**); 66%, *trans* : *cis* = 95 : 5 (**1b**); 70%, *trans* : *cis* = 91 : 9 (**1c**); 1%, *trans* : *cis* ratio not determined (**1d**); 21%, *trans* : *cis* = 79 : 21 (**1e**).
21 Note that although ethanol and methanol are not typical "green" solvents due to their flammability and toxicity (in the case of MeOH), they represent a better alternative than other organic solvents since they can be produced from biomass. See, for example: (*a*) K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M. Stefaniak, *Green Chem.*, 2008, **10**, 31; (*b*) F. M. Kerton, in *Alternative Solvents for Green Chemistry*, RSC Publishing: Cambridge, 2009.

