## Cyclisation of citronellal over heterogeneous inorganic fluorides—highly chemo- and diastereoselective catalysts for $(\pm)$ -isopulegol

Simona M. Coman,<sup>ab</sup> Pratap Patil,<sup>a</sup> Stefan Wuttke<sup>a</sup> and Erhard Kemnitz<sup>\*a</sup>

Received (in Cambridge, UK) 6th October 2008, Accepted 30th October 2008 First published as an Advance Article on the web 1st December 2008 DOI: 10.1039/b817572a

Based on a fluorolytic sol-gel synthesis, nanoscopic metal fluorides and partly hydroxylated metal fluorides were synthesized; varying the F : OH ratio inside these solids yielded catalysts with different combinations and variable strength Lewis and Brønsted acid sites, which demonstrated unexpected catalytic properties for the diastereoselective synthesis of  $(\pm)$ -isopulegol.

The world's largest demand for menthol exists among the mint products widely used in pharmaceuticals, agrochemicals, cosmetics and flavouring applications.<sup>1</sup> Among the four pairs of optical menthol isomers, only (–)-menthol exhibits the characteristic peppermint odour, and exerts a unique cooling sensation on the skin and mucous membranes. Nevertheless, racemic ( $\pm$ )-menthol also has industrial applications, although its refreshing effect is lower than that of (–)-menthol alone.

On an industrial level, one of the major routes to menthol is the Takasago process, which involves, as one of the key steps, the isomerization of (+)-citronellal to (-)-isopulegol with an aqueous ZnBr<sub>2</sub> catalyst.<sup>2,3</sup> As only (-)-isopulegol affords the correct (-)-menthol configuration during its selective hydrogenation, its synthesis from (+)-citronellal requires a high diastereoselectivity (ds).

Although heterogeneous catalysts are more attractive, almost all of those reported are less selective and form all four isopulegol isomers, as well as having a ds for  $(\pm)$ -isopulegol of 52–75%. Therefore, much attention has been paid to the search for highly active and diastereoselective heterogeneous catalysts for the cyclization of citronellal.<sup>4–6</sup> Thus, a recent report by Corma and Renz<sup>7</sup> showed that Sn-beta zeolite catalyses the cyclisation of citronellal in aceto-nitrile with a ds for  $(\pm)$ -isopulegol of 85%. Chuah *et al.*<sup>5</sup> also showed that over a Zr-beta zeolite catalyst, the cyclisation of citronellal takes place with a high ds for  $(\pm)$ -isopulegol (93%).

Recently, we have found and developed novel nanoscopic, partly hydroxylated inorganic fluorides with bi-acidic (Lewis/ Brønsted) properties.<sup>8</sup> The catalysts' synthesis follows the classical sol–gel route for high surface metal fluorides (characterised by pure Lewis acidity)<sup>9</sup> and a modified sol–gel route, in which selective solvolysis of the original M–OR bond by an aqueous HF solution results preferably in M–F, and to a minor extent, M–OH bond formation. Thus, Lewis acid sites (partly coordinated metal) and Brønsted sites (acidic M–OH groups) are formed. Both types of acid site (Brønsted/Lewis) can be tuned over a wide range by applying different molar ratios of HF to H<sub>2</sub>O during the modified sol–gel synthesis.<sup>8</sup> We have already successfully applied this type of catalyst to the synthesis of (all-*rac*)-[ $\alpha$ ]-tocopherol, <sup>8,10</sup> and will show here that they can also be applied as new active and highly diastereoselective catalysts for the cyclisation of citronellal to ( $\pm$ )-isopulegol (Scheme 1).

The catalysts were synthesised as reported elsewhere.8-11

HS-AlF<sub>3</sub> was synthesised through the sol–gel route for high surface metal fluorides<sup>11</sup> using anhydrous HF, while AlF<sub>3</sub>-H was synthesised using aqueous HF solutions with a concentration of 50 wt% HF.<sup>10</sup> The last procedure was also applied to the preparation of MgF<sub>2</sub>-40, MgF<sub>2</sub>-57, MgF<sub>2</sub>-71, MgF<sub>2</sub>-87 and MgF<sub>2</sub>-100 samples using an aqueous HF solution, with concentrations of 40, 57, 71, 87 and 100 wt% HF, respectively.<sup>8</sup> Activity tests in batch mode were carried out, as described in the following procedure: racemic citronellal (5.6 mmol, 860 mg) was dissolved in 5 ml of solvent (toluene, cyclohexane, *n*-heptane, *i*-propanol). The catalyst (50 mg) was added to this mixture, and it was then heated to 40, 60 or 80 °C with stirring for 1–6 h. After the reaction, the catalyst was filtered off and the reaction mixture analysed by GC, and <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy.

All samples were X-ray amorphous and exhibited high surface areas connected with their mesopores. Nevertheless, the acidic properties, *e.g.* the nature, the strengths and the densities of their acidic sites, were quite different, as a function of the preparation method (Table 1).<sup>8,10</sup>

The cyclisation of citronellal to isopulegol is catalysed by Lewis<sup>7</sup> and/or Brønsted<sup>12</sup> acid sites, but according to Chuah *et al.*,<sup>13</sup> the desired heterogeneous catalysts for citronellal cyclisation should have strong Lewis and weak Brønsted acidity.

An initial screening of the catalysts showed that the HS-AlF<sub>3</sub> sample was the most active and selective catalyst among the tested samples (Table 2). Therefore, in the presence of this sample, the conversion was almost complete after 1 h, and the desired product—isopulegol—was obtained with a selectivity of 90.4%. Among the four isopulegol isomers, only (±)-isopulegol and (±)-neo-isopulegol were identified by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy,† in a ratio of 85.5 : 14.5 (Table 2, entry 1).

Recently, using IR spectroscopic investigations of CO adsorption at surfaces, we showed that  $HS-AlF_3$  displays a large number of very strong Lewis acid sites with just a few weak



(rac)-citronellal (rac)-isopulegol (rac)-iso-isopulegol (rac)-neo-isopulegol (rac)-neo-isopulegol (rac)-neo-isopulegol

Scheme 1 The cyclisation of citronellal to isopulegols.

<sup>&</sup>lt;sup>a</sup> Humboldt-Universität zu Berlin, Institut für Chemie, Brook-Taylor-Straße 2, D-12489 Berlin, Germany.

E-mail: erhard.kemnitz@chemie.hu-berlin.de; Fax: +49 3020937277 <sup>b</sup> University of Bucharest, Faculty of Chemistry, Department of Chemical Technology and Catalysis, Bdul Regina Elisabeta 4-12, 030016 Bucharest, Romania

 Table 1
 Textural and chemical characterisation of the catalysts

Entry	Catalyst	BET surface area/m <sup>2</sup> g <sup>-1</sup>	Pore size/Å	Quantity of AS/mmol $g^{-1a}$	Number of $AS/\times 10^{17} m^{-2b}$
1	HS-AlF <sub>3</sub>	323	107	0.978	18.2
2	AlF <sub>3</sub> -H	187	65	0.624	20.0
3	$MgF_2-40$	180	23	0.168	5.4
4	$MgF_2-57$	235	25	0.262	6.6
5	$MgF_2-71$	276	24	0.163	3.6
6	MgF <sub>2</sub> -87	424	23	0.332	4.8
7	$MgF_2-100$	372	20	0.537	8.4
<sup><i>a</i></sup> AS <sup><i>b</i></sup> Calc	<ul> <li>acidic</li> <li>ulated from</li> </ul>	sites. Determ NH <sub>3</sub> -TPD m	ined fi easurer	rom $NH_3$ -TPD nents and $N_2$ so	measurements. rption isotherms.

**Table 2** Comparison of the catalysts in terms of conversion (X), yield (Y), selectivity (S) and diastereoselectivity (ds)<sup>*a*</sup>

Entry	Catalyst	X (%)	Y(%)	S (%)	ds (%)
1 <sup>b</sup>	HS-AlF <sub>3</sub>	99.1	89.6	90.4	85.5
2	AlF <sub>3</sub> -H	94.7	80.0	84.4	83.3
3	$MgF_2-40$	24.3	18.2	75.1	75.3
4	$MgF_2-57$	46.6	35.6	76.4	78.7
5	$MgF_2-71$	95.0	82.6	87.0	84.7
6	$MgF_2-87$	5.7	0.9	16.0	>99.0
7	$MgF_2-100$	3.0	1.1	36.7	>99.0
<sup><i>a</i></sup> Reactic	on conditions: 8 al/catalyst mola	360 mg citro r ratio = 18	onellal, 5 ml $30:1, {}^{b}1$ h	toluene, 6	h, 80 °C;

Lewis acid sites at the surface.<sup>14</sup> Interestingly enough, during the course of these measurements, it turned out that handling this solid, very strong Lewis acid in air (several seconds for sample preparation) created weak Brønsted acid sites at the surface due to the interaction of the very strong Lewis acid sites with water molecules from airborne moisture. However, these weak Brønsted acid sites could be reversibly converted into Lewis acid sites by an appropriate thermal treatment at around 300 °C. Since the HS-AlF<sub>3</sub> samples used in our catalytic reactions were stored and handled in air, they consequently provided—beside very strong Lewis sites.

On the other hand, an IR spectrum of AlF<sub>3</sub>-H immediately displays two bands: an intensive band assigned to medium Brønsted acid sites  $(2172 \text{ cm}^{-1})$  and a band assigned to strong Lewis acid sites (2207  $\text{cm}^{-1}$ ), which only develops as a small feature.<sup>10</sup> Therefore, the Lewis : Brønsted acid site ratio is quite small. As long as both samples display a similar number of acid sites (Table 1, entries 1 and 2) per square metre, the catalytic performance of these two samples can be explained in terms of the different nature of their acidity (Lewis/Brønsted) and their acidity strength. Therefore, in accordance with Chuah et al.,<sup>13</sup> the desired heterogeneous catalysts for citronellal cyclisation should have strong Lewis and weak Brønsted acidity, which is perfectly fulfilled in case of HS-AlF<sub>3</sub>. Nevertheless, the activity and selectivity of AlF<sub>3</sub>-H is only slightly lower than that of HS-AlF<sub>3</sub> (Table 2, entry 2). Therefore, we cannot neglect a cyclization mechanism based on almost exclusively medium Brønsted acid sites.

In the case of the  $MgF_2$  sample series, the best results were obtained in the presence of  $MgF_2$ -71 (Table 2, entry 5). Pyridine-IR measurements show that all of the catalysts in the  $MgF_2$  series are characterised by the simultaneous presence of Lewis and Brønsted acid sites, in different amounts

but of a similar strength (Fig. 1). Furthermore, CO-IR investigations of these samples showed that both sites are centres of medium strength.<sup>8</sup>

MgF<sub>2</sub>-100 and MgF<sub>2</sub>-87 samples, also characterised by the predominant presence of Lewis acid sites, with only a few Brønsted acid sites on the surface, are significantly less active and selective for isopulegols than HS-AlF<sub>3</sub> (Table 2, entries 1, 6 and 7). Their low catalytic performances are due to two important parameters: the density and the strength of their acid sites, both of them being at the opposite end of the scale compared to HS-AlF<sub>3</sub>. On the other hand, the ds for ( $\pm$ )-isopulegol is almost 100% (Table 2, entry 7). The high ds observed for this sample may be due to steric hindrance imposed by the catalyst's pore diameter, the most favored geometrical diastereomers of isopulegols being formed in excess (Table 1, entries 1 and 7). A similar effect of pore size upon the ds was also observed by Murzin *et al.*<sup>15</sup>

The fine tuning of Lewis/Brønsted acid site ratios seems to be essential for this synthesis (Table 2, entries 3–7). Therefore, the existence of a predominant density of Brønsted acid sites (MgF<sub>2</sub>-40) leads to a relatively low yield of isopulegols, while the absence of Brønsted acid sites (or only a very low density of these) makes MgF<sub>2</sub>-100 and MgF<sub>2</sub>-87 almost non-active. On the other hand, irrespective of the catalysts' nature, the ds for ( $\pm$ )-isopulegol is higher than 75%, the value characteristic of a thermodynamic equilibrium of an isopulegol mixture. Contrary to the statement of Ravasio *et al.*,<sup>16</sup> who claimed a correlation between the stereoselectivity for (–)-isopulegol and the strength of the Lewis acid sites, in our case, there seemed to be no relationship between these two parameters.

The activity, overall selectivity and isomer distribution were also affected by the solvent polarity, reaction temperature and amount of citronellal used in the reaction. Table 3 compiles the solvents that were used in this study, taking HS-AlF<sub>3</sub> as the example. After 1 h, the conversion of citronellal was lower than 34% in *i*-propanol, but higher than 99% in toluene



Fig. 1 Infrared spectra (Py-IR) of the sol–gel nanoscopic  $\mbox{MgF}_2$  samples.

**Table 3** The influence of the solvent's nature upon  $\text{HS-AlF}_3$  catalytic performance<sup>*a*</sup>

Entry	Solvent	Dielectric constant (ε)	X(%)	Y(%)	S (%)	ds (%)
1	Toluene	2.40	99.1	89.6	90.4	85.5
2	Cyclohexane	2.02	86.0	81.2	94.4	84.0
3	<i>n</i> -Heptane	1.92	87.3	81.0	92.9	89.3
4	<i>i</i> -Propanol	20.30	33.7	26.5	78.5	28.3
<sup>4</sup> Reac	tion conditions	20.30 : 860 mg citro	nellal. 5	20.5 ml of sol	78.5 vent. 1 ł	28.5 1. 80 °C

citronellal/catalyst molar ratio = 180 : 1.

(Table 3, entries 1 and 4). The selectivity followed the same trend as the conversion; the values obtained in non-polar media being higher than in polar media. A better definition of polarity should take into account the strength of adsorption of a substrate onto an adsorbent material (Snyder's eluotropic series).<sup>17</sup> Strong solvent adsorption site interactions generate strong competition between the substrate and solvent for these sites. Therefore, as the HS-AlF<sub>3</sub> catalyst is a very strong Lewis acid, the predominant adsorption of *i*-propanol renders the active site inaccessible to substrates, and consequently results in a low concentration of them on the catalytic surface. Consequently, a weak interaction between the solvent (*i.e.*, non-polar solvents) and the catalyst surface allows a higher concentration of the substrate to be adsorbed onto the catalyst surface, and implicitly leads to a faster reaction. The decrease in selectivity for isopulegols in *i*-propanol (Table 3, entry 4) can be explained by the citronellal reduction to citronellol in the Meerwein-Ponndorf-Verley (MPV) reaction and the subsequent dehydration of the products.<sup>18</sup>

The results obtained in different solvents were also confirmed by tests with different concentrations of substrate solution. Therefore, when the substrate concentration increased from 9 to 16.5 and 23 wt%, the TON increased from ca. 56 to 112 and 165, respectively.

One attempt to improve ds values by lowering the reaction temperature, as has been done successfully in other cases,<sup>19</sup> did not result in any significant improvement. Decreasing the temperature from 80 to 40 °C slight decreased the selectivity obtained (from 91.8 to 88.3%) in the case of HS-AlF<sub>3</sub>, but the conversion decreased significantly (from 99.3 to 41.6%). The best results in terms of selectivity for isopulegols and ds for ( $\pm$ )-isopulegol were obtained at 60 °C, while the conversion remained more or less at the same level (X = 97.4%, S = 92.3%, ds = 91.7%).

In summary, nanosized inorganic fluoride catalysts have been employed for the first time in intramolecular carbonyl-ene reactions. Their catalytic performance was influenced by both the ratio and strength of their Brønsted/Lewis acid sites, and the reaction conditions. Therefore, the best activities and selectivities for isopulegols were obtained in the presence of catalysts with very strong Lewis and weak Brønsted acidities. This optimum ratio could be adjusted by tuning the HF : H<sub>2</sub>O ratio during the synthesis. The ds for ( $\pm$ )-isopulegol was superior (91.7%) to most conventional heterogeneous catalysts used for this reaction and seems also to be influenced by the textural properties of the catalyst.

Dr S. M. Coman is a fellow of the Alexander von Humboldt Foundation.

## Notes and references

† <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>). Isopulegol: 4.87 (m, C<sup>10</sup>H*H*, *cis* to CH<sub>3</sub>, 1H), 4.83 (s, C<sup>10</sup>*H*H, *trans* to CH<sub>3</sub>, 1H), 3.43 (dt, C<sup>3</sup>*H*(OH), J = 10.4 and 4.3 Hz, 1H), 2.03 (m, C<sup>2</sup>*H*H, 1H), 1.86 (m, C<sup>4</sup>*H*, 1H), 1.69 (d, C<sup>9</sup>H<sub>3</sub>, J = 0.5 Hz, 3H), 1.65 (m, C<sup>5</sup>*H*H, C<sup>6</sup>*H*H, 2H), 1.49 (m, C<sup>1</sup>*H*, 2H), 1.32 (m, C<sup>5</sup>H*H*, 1H), 0.97 (m, C<sup>2</sup>H*H*, C<sup>6</sup>H*H*, 2H) and 0.92 (d, C<sup>7</sup>H<sub>3</sub>, J = 6.5 Hz, 3H). Neo-isopulegol: 3.67 (dt, C<sup>3</sup>*H*(OH), J = 10.4 and 4.2 Hz, 1H).

- 1 G. S. Clark, Menthol, Perfumer Flavorist, 1998, 25, 33.
- 2 Y. Nakatani and K. Kawashima, Synthesis, 1978, 147.
- 3 S. Otsuka and K. Tani, Synthesis, 1991, 665.
- 4 C. Milone, A. Parri, A. Pistone, G. Neri and S. Galvagno, *Appl. Catal.*, *A*, 2002, **233**, 151.
- 5 Z. Yongzhong, N. Yuntong, S. Jaenicke and G. K. Chuah, J. Catal., 2005, 229, 404.
- 6 K. Arata and C. Matsuura, Chem. Lett., 1989, 1788.
- 7 A. Corma and M. Renz, Chem. Commun., 2004, 550.
- 8 S. Wuttke, S. M. Coman, G. Scholz, H. Kirmse, A. Vimont, M. Daturi, S. L. M. Schroeder and E. Kemnitz, *Chem.-Eur. J.*, DOI: 10.1002/chem.200801702.
- 9 S. Rüdiger, U. Groß and E. Kemnitz, J. Fluorine Chem., 2007, 128, 353.
- 10 S. M. Coman, S. Wuttke, A. Vimont, M. Daturi and E. Kemnitz, Adv. Synth. Catal., 350, 2517.
- 11 E. Kemnitz, U. Groß, S. Rüdiger and C. S. Shekar, Angew. Chem., Int. Ed., 2003, 42, 4251.
- 12 D.-L. Shieh, C.-C. Tsai and A.-N. Ko, React. Kinet. Catal. Lett., 2003, 79, 381.
- 13 G. K. Chuah, S. H. Liu, S. Jaenicke and L. J. Harrison, J. Catal., 2001, 200, 352.
- 14 T. Krahl, A. Vimont, G. Eltanany, M. Daturi and E. Kemnitz, J. Phys. Chem. C, 2007, 111, 18317.
- 15 P. Maki-Arvela, N. Kumar, V. Nieminen, R. Sjoholm, T. Salmi and D. Y. Murzin, J. Catal., 2004, 225, 155.
- 16 N. Ravasio, M. Antenori, F. Babudri and M. Gargano, Stud. Surf. Sci. Catal., 1997, 108, 625.
- 17 Y.-M. Chung and H.-K. Rhee, J. Mol. Catal. A: Chem., 2001, 175, 249.
- 18 Z. Yongzhong, N. Yuntong, S. Jaenicke and G.-K. Chuah, J. Catal., 2005, 229, 404.
- 19 V. K. Aggarwal, G. P. Vennall, P. N. Davy and C. Newman, *Tetrahedron*, 1998, **39**, 1997.