Friedel–Crafts alkylation in supercritical fluids: continuous, selective and clean

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Continuous Friedel–Crafts alkylation of mesitylene, $C_6H_3Me_3$, and anisole, C_6H_5OMe, with propene or propan-2-ol has been carried out in supercritical propene or CO_2 using a heterogeneous polysiloxane-supported solid acid Deloxan® catalyst in a small fixed bed reactor (10 ml volume); 100% selectivity for mono-alkylated products with 50% conversion could be obtained by adjusting the reaction parameters, *e.g.* temperature, pressure, flow rates, *etc.*

Numerous chemical syntheses involve Friedel–Crafts or Friedel–Crafts-type alkylation reactions, both on laboratory and industrial scales. Friedel–Crafts chemistry is therefore of major importance and research in this field is of continuing chemical interest.[1–5] Frequently, the reaction is used to add only a *single* alkyl group to the substrate, but addition of the first alkyl group activates the substrate so that subsequent alkylation is made easier. Thus, conditions have to be controlled precisely, often with long reaction times and low temperatures, to minimise the formation of poly-alkylated by-products.

Friedel–Crafts reactions are usually carried out batch-wise in a large excess of the substrate or in an organic solvent. Generally, the reaction is carried out in the presence of Lewis acid catalysts (*e.g.* $AlCl_3$, BF_3, $TiCl_4$) or strong protic acids (*e.g.* HF, H_2SO_4). Relatively high concentrations of catalyst are needed; often the amounts are near stoichiometric, especially when H_2O is generated. These problems make most Friedel–Crafts processes inherently dirty. Therefore, the development of environmetally more benign Friedel–Crafts processes is a high priority. Solid acid catalysts based on clays, zeolites or even graphite[6] could be the answer to *cleaner* Friedel–Crafts chemistry, but until recently rapid catalyst deactivation has prevented the development of a commercial process.[7] Not only can solid catalysts be easily separated from liquid products, they also offer the possibility of carrying out Friedel–Crafts reactions in continuous rather than batch reactors.[8] Continuous flow reactors can be smaller than the batch reactors needed to generate comparable amounts of product.[9] A reactor of smaller size usually increases safety and reduces capital cost.

Very recently, we described[10] how the supercritical hydrogenation of a wide a range of organic compounds can be carried out extremely efficiently in small-scale *continuous* flow reactors (5 or 10 ml) using Pd and Pt heterogeneous catalysts supported on polysiloxane (Deloxan®, Degussa AG). Here we show how the *same* reactor can be used to carry out continuous Friedel–Crafts alkylation using a commercially available solid

acid catalyst based on the *same* Deloxan® support.‡ In our process,§ the organic solvent is replaced by a supercritical fluid, *e.g.* $scCO_2$. The separation of the product occurs simply by expanding the fluid to atmospheric pressure, so the crude product can be analysed without further work-up. Although reaction temperatures are high, because of short residence times, our process maintains high product selectivity.

Our initial reactions involved mesitylene **1** ($C_6H_3Me_3$) with propene **2**, which acts both as alkylating agent and as supercritical solvent [scPropene, $T_c = 91.9$ °C, $p_c = 46.0$ bar (10 bar = 1 MPa)]. This reaction was chosen because the mono-**3**, di- **4** and tri-alkylated product **5** each have only *one* possible isomer (Scheme 1), which simplifies product analysis.¶

Table 1 shows that Friedel–Crafts chemistry can indeed be carried out *continuously* under these conditions. The selectivity is reasonable for 1-isopropyl-2,4,6-trimethylbenzene **3** but significant amounts of **4** and dimers of propene **2** are formed. Table 1 also shows that the yield of **3** cannot easily be improved by varying the reaction conditions.

By contrast, selectivity for the formation of **3** is much higher in the alkylation of **1** with propan-2-ol, **6**, in supercritical CO_2 ($scCO_2$, $T_c = 31.1$ °C, $p_c = 73.8$ bar) using the same solid acid Deloxan® catalyst. The reaction forms water but this is not a serious problem; the organic and water layers are easily separated after the $scCO_2$ has been vented. Initially, the reaction was carried out with a three-fold excess of **6** over **1** (total flow rate of **1** + **6**: 0.50 ml min^{-1}) at 220 bar and $T_{cat} = 200$ °C with a gaseous CO_2 flow rate of 0.43 l min^{-1}. Analysis of the organic layer showed that the conversion of **1** was 46% with **3** as the major product (40% yield). As side-products, **4** was found in 5% yield along with traces of diisopropyl ether (1%). Table 2 summarises the results obtained by varying the reaction conditions. The yield of **3** can be improved by optimising the temperature and raising the pressure. When **1** is in excess, **3** *is the only detectable organic product.*

Previous attempts to run *continuous* Friedel–Crafts alkylation have frequently been thwarted by poor catalyst lifetimes but the lifetime of the Deloxan® catalyst is relatively long. In fact, when the reaction was started using a *fresh* sample of ASP I/7 acid Deloxan® catalyst, the activity actually increased after an induction period of *ca.* 100 min and was maintained for at least a further 15 h operation. We initially attributed this induction to some activating effect of the H_2O formed in the reaction. However, the yields of **3** were dramatically lower

Scheme 1

Table 1 Alkylation of mesitylene **1** with propene **2** at 200 bar pressure[a]

| T_{cat}/°C | Flow rate of **1**/ ml min^{-1} | Flow rate[b] of propene | Yield (%) | | | | | |
			1	**3**	**4**	**5**	Dimers of **2**	Trimers of **2**
160	0.30	0.65	57	25	6	0	12	0
160	0.30	0.43	47	25	10	0	14	4
180	0.30	0.43	32	27	14	2	16	9

[a] The reaction was carried out in a heated reactor of 10 ml volume containing 9 ml of the solid acid Deloxan® catalyst (ASP I/7, particle size: 0.1–0.4 mm). No reaction was observed when the catalyst was replaced by Nafion as the solid acid. [b] Flow rate of propene in 1 min^{-1} measured at 1 atm and 20 °C, as determined by bubble flow meter.
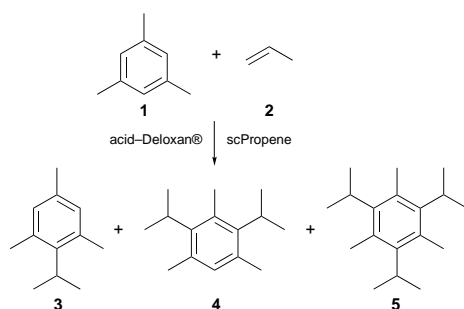
Table 2 Investigation[a] of (I) temperature, (II) pressure and (III) molar ratio on yield of **3**

	Molar ratio of **1**:**6**	Flow rate of **1** + **6**/ g min^{-1}	T_{cat}/°C	p CO$_2$/bar	Found[b] **3** (%)	Yield[c] of **3** (%)	Production rate of **3**/g min^{-1}
I	2.0:1.0	0.60	200	200	15.0	30.0	0.09
	2.0:1.0	0.60	230	200	21.0	42.0	0.13
	2.0:1.0	0.60	250	200	21.0	42.0	0.13
	2.0:1.0	0.60	270	200	15.0	30.0	0.09
	2.0:1.0	0.60	300	200	7.5	15.0	0.05
II	2.0:1.0	0.60	250	200	21.0	42.0	0.13
	2.0:1.0	0.60	250	150	18.5	37.0	0.11
	2.0:1.0	0.60	250	100	16.0	32.0	0.10
III	1.0:5.0	1.51	250	150	19.0[d]	19.0[d]	0.29
	2.0:1.0	0.60	250	150	18.5	37.0	0.11
	5.0:1.0	0.52	250	150	10.0	50.0	0.05

[a] All reactions carried out in scCO$_2$ (0.65 l min^{-1}) with **3** as the only detectable product. [b] Product analysis was by ^{1}H NMR spectroscopy (CDCl$_3$). [c] Based on the amount of **6** in the initial reaction mixture. [d] Yield based on **1**. In addition, 3% of **4** and traces of side-products were found.

Scheme 2
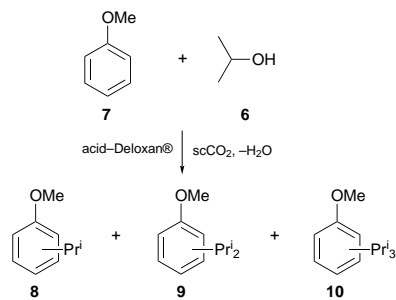
when the catalyst was conditioned with water for 30 min prior to use. When operated for maximum flow of **3** (see Table 2) the catalyst can produce twice its volume of **3** per hour.

The supercritical reactor can also be applied sucessfully to the continous alkylation of anisole **7** by scPropene **2** or by propan-2-ol **6** in scCO$_2$ (Scheme 2). As with the alkylation of **1**, there is significant selectivity in favour of the mono-alkylated product. Thus, **6** reacted with **7** at a molar ratio of 1.0:3.0 to form isomers of **8** (30% yield) and **9** (*only* 6% yield).‖ No further products could be detected by GC–MS. When **7** was alkylated at a flow rate of 0.2 ml min^{-1} with scPropene (flow rate of gaseous propene: 0.43 l min^{-1}) under the same conditions, the yield of **8** was 38% with the same isomer ratio as was found with propan-2-ol.‖ However, the yield of **9** increased to 18% (three isomers at a ratio of 5:2:1). In addition, **10** was found in 5% yield (peak ratio 5:2 at a mass of 234) as well as trace amounts (3%) of propene di- and tri-mers.

The supercritical fluid probably plays several roles in these reactions. Compared to liquid phase reactions, the fluid reduces mass transport restrictions at the surface of the catalyst. Compared to a gas phase reaction, it increases the density of the reaction medium and hence increases the residence time of the substrate in a given size of reactor. This allows continuous alkylation to be caried out on a reasonable scale in a small reactor. Finally, it may reduce coking of the catalyst preventing premature deactivation of the catalytic sites.

This investigation has shown that aromatic substrates can undergo *continuous and sustainable* Friedel–Crafts alkylation in supercritical fluid solution over solid acid heterogeneous catalysts. The reactions can be carried out in a flow reactor, which differs only in the peripheral pipework from that used for the supercritical hydrogenation of organic compounds.[10] The method of alkylation has features of potential importance for the manufacture of fine chemicals. It is selective, organic solvents are eliminated and a *clean* heterogeneous catalyst replaces a liquid–based system. Thus, supercritical alkylation is a step closer to ennvironmentally acceptable Friedel–Crafts chemistry.

Notes and References

† Web page: http://www.nottingham.ac.uk/supercritical/

‡ Deloxan® ASP catalysts (ref. 11) are specially designed polysiloxane based solid acids, formed by sol-gel condensation of alkyl sulfonic acid functionalized organosilane monomers, *e.g.* HO$_3$SCH$_2$CH$_2$CH$_2$Si(OH)$_3$, which overcome the drawbacks of organic polymers by virtue of their inert matrix material and excellent compatability with almost all organic solvents. The sol-gel process yields products with a relatively narrow particle size distribution, high porosity, large pore diameters (> 20 nm) and high BET surface areas (300–600 m^2 g^{-1}).

§ The substrate, reactant and supercritical fluid are brought together in a heated mixer, passed through the hot reactor (10 ml volume; 9 mm i.d., length 152 mm) containing the catalyst, and then expanded to separate the product from the fluid. The reactor is assembled from commercially available units: scCO$_2$ and scPropene pump PM 101 and Expansion Module PE 103 (all from NWA GmbH, Lörrach, Germany), a high pressure mixer (Medimix) and Gilson pumps 303, 305 (for substrate and reactant). *SAFETY NOTE: Reactions in supercritical fluids involve high pressures and should only be carried out with appropriate equipment.*

¶ Product analysis by GC–MS or ^{1}H NMR spectroscopy.

‖ Pressure, 220 bar; catalyst temperature, 200 °C, flow rate of gaseous CO$_2$ of 0.2 l min^{-1}; total flow rate of **6** + **7**, 1.0 ml min^{-1}. The product analysis is more complicated for the reactions of **7** than for those of **1** becasue the products (**8**, **9** and **10**) all have more than one possible isomer. Thus, GC–MS gave *three* peaks for **8** (*m/z* 150) in the ratio of 13:12:1, corresponding to the *ortho*, *para* and *meta* isomers. Similarly, *two* peaks (*m/z* 192) were found in the ratio 4:1 for the isomers of **9**.

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