Chloroindate(III) ionic liquids: recyclable media for Friedel–Crafts acylation reactions

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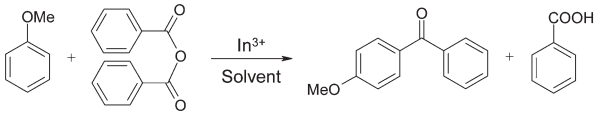
Chloroindate(III) ionic liquids are versatile reaction media for Friedel–Crafts acylation reactions; the system is catalytic and totally recyclable, using an aqueous workup, with no leaching of the indium into the product phase.

Friedel–Crafts acylation reactions are used extensively in the pharmaceutical and fine chemicals industry for the synthesis of aromatic ketones. Traditionally, the catalyst of choice for the reaction is a strong Lewis acid, such as anhydrous aluminium(III) chloride in an organic solvent;[1] however, once the ketone product is formed, the carbonyl group strongly bonds to the Lewis acid rendering the "catalyst" inactive. A range of other Lewis acid and Brønsted acid Friedel–Crafts catalysts have been reported with a variety of success, including zeolites,[2] HF,[3] triflate salts,[4] and metal bis{(trifluoromethyl)sulfonyl}amide compounds.[5] In addition, strongly Lewis acidic chloroaluminate(III) ionic liquids have been reported; however, these suffer from the same issues as anhydrous aluminium(III) chloride.[6,7] More recently, ionic liquids based on other combinations of metal chlorides with organic halides have been reported.[8] Of particular interest to Friedel–Crafts reactions, aluminium(III) chloride may be replaced by indium(III) chloride to form chloroindate(III) ionic liquids.[9–11]

Indium(III) species have been used as Lewis-acid catalysts in a variety of reactions and the use of indium halides in organic synthesis has recently been reviewed.[12] The advantage of indium(III) chloride methodology, compared with aluminium(III) chloride, is its hydrolytic stability and reduced oxophilicity. By combining the indium(III) chloride with an organic halide salt, ionic liquids can be formed with good solvating ability and negligible vapour pressure, as well as the liquid being both inherently Lewis-acidic and water stable in contrast to the analogous chloroaluminate systems.[7,8]

Chloroindate(III) ionic liquids are synthesised by mixing the appropriate amounts of the organic chloride salt, in this paper 1-butyl-3-methylimidazolium chloride ([C_4mim]Cl) or trihexyltetradecylphosphonium chloride ([$P_{6,6,6,14}$]Cl), with anhydrous indium(III) chloride at 80 °C.† The resulting ionic liquids were used without further treatment in the Friedel–Crafts acylation reaction. As with chloroaluminate ionic liquids, acidic, neutral and basic chloroindate(III) ionic liquids are formed by varying the organic chloride to indium(III) chloride ratio.‡ In this paper we report the first reactions (outside of the patent literature)[9] to be performed in acidic chloroindate(III) ionic liquids using Friedel–Crafts acylation as the example.

Fig. 1 shows the time dependence for the benzoylation of anisole with benzoic anhydride (1) using a chloroindate(III) ionic liquid based on $InCl_3$-[C_4mim]Cl $\{X(InCl_3) = 0.67\}$† compared with using indium(III) chloride alone as the catalyst in no solvent, 1,2-dichloroethane or the ionic liquid 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)amide ([C_4mim][NTf_2]). Where indium(III) chloride alone was used as the catalyst, 5 mol% with respect to the anisole, was employed. To enable a direct comparison, the amount of chloroindate(III) melt used was calculated so that the molar excess of indium(III) chloride compared with [C_4mim]Cl was also 5 mol% with respect to the anisole, herein denoted as $\xi = 5$. All the reactions were performed at 80 °C to ensure that the reagents and the chloroindate(III) ionic liquid were liquid throughout the course of the reaction.



(1)

The best yield of 4-methoxybenzophenone is obtained when indium(III) chloride is used in conjunction with ionic liquids either as a solution in [C_4mim][NTf_2] or as the chloroindate(III) binary ionic liquid $\{X(InCl_3) = 0.67\}$. A solution of indium(III) chloride in the water-miscible ionic liquids [C_4mim][OTf] and [C_4mim][BF_4] showed no activity for this reaction. This has been reported previously for other Friedel–Crafts reactions performed in ionic liquids.[13] Although this may be associated with higher amounts of residual water in the hydrophilic ionic liquids compared with the hydrophobic ionic liquids, the results of anion exchange cannot be

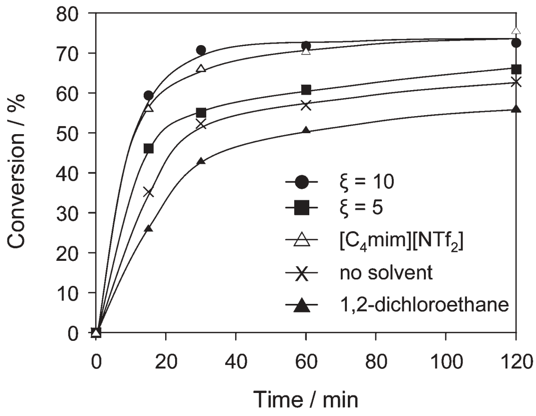


Fig. 1 Comparison of the percentage conversion for the benzoylation of anisole with benzoic anhydride using indium(III) chloride in 1,2-dichloroethane and [C_4mim][NTf_2] and in the absence of a solvent, and using $InCl_3$-[C_4mim]Cl $\{X(InCl_3) = 0.67; \xi = 5 \text{ or } 10\}$ at 80 °C.

discounted. It is known, for example, that metal bis(trifluoromethanesulfonyl)amides are, in general, much more active than the corresponding triflate salts.[14] In 1,4-dioxane, again no conversion to product was found, presumably due to deactivation of the indium(III) chloride by complexation with 1,4-dioxane. As expected, increasing the volume of the ionic liquid, such that $\xi = 10$, resulted in a higher rate of reaction. In addition, neither basic nor neutral chloroindate ionic liquids were found to catalyse the reaction. This is also the case with aluminium(III) chloride sytstems.[6,7] The shape of the conversion *versus* time curves shown in Fig. 1 is indicative of the catalyst being deactivated. In similar reactions, it has been shown that the addition of 4-methoxybenzophenone reduces the reaction rate but benzoic acid had no effect.[15] The latter is due to the poor solubility of the acid in the ionic liquid.

Although the chloroindate(III) system requires more indium(III) chloride to produce an effective catalytic system than, for example, indium(III) chloride dissolved directly in [C$_4$mim][NTf$_2$], the workup and recycle of the reaction are significantly more efficient. In [C$_4$mim][NTf$_2$], the product can be removed by solvent extraction using, for example, mesitylene; however, the extraction efficiency is poor due to the strong affinity of the ketone product with the ionic liquid. For the chloroindate(III) system, an aqueous workup is possible. To recycle the chloroindate(III) system, the minimum amount of solvent, which could be the anisole starting material, was added to the reaction mixture in order to ensure that the solution became homogeneous. Water was then added and separated by decantation which removes the ionic liquid and this phase is subsequently dehydrated to recover the ionic liquid. The products were then separated by washing the anisole phase with hot aqueous NaOH to remove the benzoic acid and the anisole recovered by distillation. Using this procedure, the reaction system was recycled 5 times with only a small loss in activity of the ionic liquid system, as shown in Table 1, and no change in selectivity. Furthermore, the indium content in the 4-methoxybenzophenone was < 0.3 µg indium/gram of product for each recycle, analysed by ICP analysis, *i.e.* < 0.00003% loss of ionic liquid. Since the small amount of indium detected by ICP is insignificant, the decrease in activity observed on recycle may be associated with mechanical losses on work up.

Friedel–Crafts acylation of a range of aromatic compounds has also been successfully performed using benzoic anhydride, benzoyl chloride and ethanoic anhydride in the chloroindate(III) ionic liquid, Table 1. Chlorobenzene and fluorobenzene were not found to react at 80 °C with benzoic anhydride; however, some reaction (*ca.* 5%) was observed at 120 °C. Using benzoyl chloride, both chlorobenzene and fluorobenzene gave excellent yields and selectivities for the 4-isomer, albeit with an increased catalyst concentration in the case of chlorobenzene. Benzene, isobutylbenzene, toluene and naphthalene all gave good yields with both benzoyl chloride and benzoic anhydride; although higher temperatures were required for the more sterically hindered isobutyl derivative. In all cases the anhydride acylating agent was less reactive, as expected, compared with the acid chloride. It is interesting to note that, in the case of naphthalene, the more bulky anhydride increased the formation of the less favoured 2-substituted product. As shown above, anisole was easily acylated with benzoic anhydride and benzoyl chloride although, as expected, the rate of reaction for anisole using ethanoic anhydride was slower in comparison. A similar reduction in rate was also observed for toluene.

Table 1 Comparison of acylation reactions using an InCl$_3$-[C$_4$mim]Cl {X(InCl$_3$) = 0.67} ionic liquid, $\xi = 5$, unless otherwise indicated, and benzoic anhydride (BA), benzoyl chloride (BC) or ethanoic anhydride (EA). With the exception of reactions performed using benzene and naphthalene, a 1.1 molar excess of acylating agent was used. For benzene and naphthalene, a 1.5 molar excess of acylating agent was used

Substrate/acylating agent	Time/h	Temp./°C	Yield/%	Selectivity (2- : 3- : 4-)
Benzene/BA	48	80	22	—
Benzene/BC	48	80	81	—
Toluene/BA	3	80	51	14 : 0 : 86
Toluene/BA	48	110	86	16 : 3 : 81
Toluene/BC[a]	18	110	93	15 : 3 : 82
Toluene/EA	48	110	2	14 : 5 : 81
Isobutylbenzene/BA	48	120	87	13 : 1 : 86
Isobutylbenzene/BC	48	120	96	16 : 1 : 83
Chlorobenzene/BC[b]	69	120	78	11 : 2 : 87
Chlorobenzene/BC[c]	96	120	75	11 : 2 : 87
Fluorobenzene/BC	96	80	96	4 : 0 : 96
Naphthalene/BA[d]	48	80	41	2 : 1[e]
Naphthalene/BC[d]	48	80	81	6 : 1[e]
Anisole/BA	3	80	79	6 : 0 : 94
Anisole/BA[f]	3	80	62	6 : 0 : 94
Anisole/BA	48	80	97	2 : 0 : 98
Anisole/EA	3	80	34	2 : 0 : 98
Anisole/EA	48	80	89	2 : 0 : 98
Anisole/BC[a]	18	100	94	6 : 0 : 94

[a] $\xi = 12.5$. [b] $\xi = 15$. [c] InCl$_3$-[P$_{6,6,6,14}$]Cl {X(InCl$_3$) = 0.67}, $\xi = 10$. [d] InCl$_3$-[C$_4$mim]Cl {X(InCl$_3$) = 0.60}, $\xi = 10$. [e] Selectivity for the 1- : 2- products. [f] 5th recycle.

It should be noted that the recycle procedure described for the benzoylation reaction mixture could not be applied to mixtures containing ethanoic anhydride due to the poor phase separation between the organic and aqueous phases. This is probably due to the presence of ethanoic acid, which is highly soluble in both phases. Due to the lower distillation temperature of methoxyacetophenone (85 °C at 0.1 mm Hg) compared with methoxybenzophenone, however, direct distillation under vacuum was possible without decomposition of the ionic liquid.

It should be noted that it is exceptionally difficult to obtain good yields in genuinely catalytic Friedel–Crafts acylation reactions with aromatic compounds less reactive than benzene.[16] With indium(III) chloride ionic liquids as catalysts, 75–96% yields were obtained with these unreactive compounds.

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Notes and references

† To anhydrous indium(III) chloride (11.3 mmol) was added 1-butyl-3-methylimidazolium chloride [C$_4$mim]Cl (5.65 mmol), and the mixture stirred under ambient atmosphere at 80 °C. This yielded chloroindate(III) ionic liquid as a mobile white suspension (the suspended material is thought to be undissolved indium(III) chloride). For reactions performed using the indium(III) chloride, typically the catalyst, solvent (1.5 cm^3) and anisole (4.6 mmol) were added. The reaction mixtures were heated to 80 °C, whilst stirring, before the addition of benzoic anhydride (5.0 mmol). The chloroindate(III) ionic liquid as prepared above (3.50 g) and anisole (113 mmol) were heated to 80 °C, whilst stirring, before the addition of benzoic anhydride (124 mmol).

‡ The composition of a chloroindate(III) ionic liquid is best described by the apparent mole fraction of $InCl_3$ $\{X(InCl_3)\}$ present. Ionic liquids with $X(InCl_3) < 0.5$ are called 'basic'; those with $X(InCl_3) > 0.5$ are called 'acidic'; melts with $X(InCl_3) = 0.5$ are called 'neutral'.

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