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Tandem catalytic condensation and hydrogenation processes in ionic liquids

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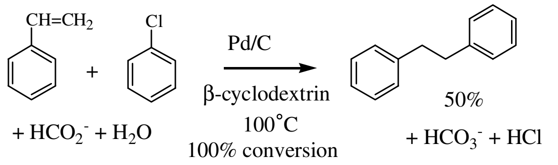
Abstract—A domino reaction composed of a Knoevenagel condensation combined with a simultaneous catalytic hydrogenation is reported in an ionic liquid solvent under mild conditions (298–363 K and 300 kPa). No interference between the catalysts (Pd/C and amine acetate salt) of the two diverse steps was monitored. The product could be neatly extracted by diethyl ether and the solvent containing the catalysts could be recycled and reused five times without any loss in activity or selectivity. The same methodology in a common organic solvent such as DMA resulted in significant competing parallel hydrogenation of the aldehyde to alcohol.

Tandem (or 'domino') reactions are highly desirable for increasing the efficiency of a synthetic route by inducing multiple transformations of a substrate in one operation with diminution in the separation and purification of intermediates.[1] The major challenge associated with the design of new catalytic domino processes is the selection of catalysts and reaction conditions in such a way that no interference or cross contamination will take place between the concurrent catalytic reactions. Utilization of unique multiphase solvent systems such as fluorous solvents[2] or ionic liquids[3] can contribute to this aim.

We were interested in merging a condensation step with a subsequent catalytic hydrogenation step to provide a methodology for a tandem synthesis of hydrocinnamic acids and other phenethyl derivatives. In a previous report[4] we have disclosed the analogous combination of a Heck reaction with a hydrogenation process to yield 1,2-diphenylethane in one (tandem) step starting with styrene and chlorobenzene (Eq. 1):



(1)

In this study we have carried out a catalytic Knoevenagel condensation of a cyanoacetate ester with various aldehydes and ketones under hydrogen pressure in the presence of palladium on carbon using ionic liquids as solvents. No disturbance was detected between the metal hydrogenation catalyst and the ammonium salt condensation catalyst and both processes proceeded smoothly in a simultaneous manner.

Ionic liquids (IL) such as 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF$_4$) or hexafluorophosphate ([bmim]PF$_6$) are very promising green solvents with unique properties such as negligible vapor pressure, formation of a separate liquid phase both with water and with common organic solvents, good capacity for solubilizing organic substrates, ease of recycling and reuse and lack of flammability.[3]

Ionic liquids have been used as solvents in homogeneous catalytic hydrogenation including asymmetric hydrogenation.[5] ILs were found to stabilize the air sensitive chiral homogeneous catalyst Rh–MeDuPHOS and in other instances were used for recovery and recycling of the catalyst.[6] Ligand protected palladium nanoparticles have also been used as hydrogenation catalysts in ionic liquids.[7]

Knoevenagel condensations are effectively conducted in an IL using ethylenediammonium diacetate (EDDA) as the catalyst.[3] Ammonium and amine salts are long known as better catalysts than the free amines in these reactions.[8]

Keywords: Knoevenagel condensation; Pd/C; Ionic liquids; Hydrogenation.

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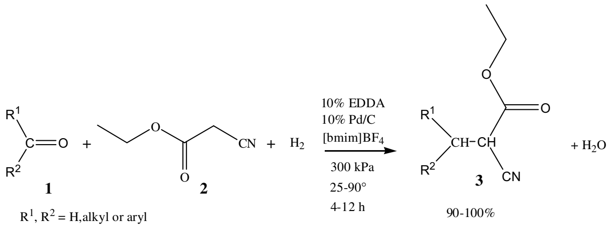
We have developed the condensation reaction of ethyl cyanoacetate with aldehydes or ketones combined with the simultaneous reduction of the C═C bond under 300 kPa pressure of dihydrogen in the presence of a mixture of the EDDA and Pd/C catalysts (Eq. 2)



(2)

Unpredictably when reaction 2 was carried out in a common organic solvent such as DMA a considerable amount of benzyl alcohol and toluene was formed by competing direct hydrogenation of the starting aldehyde. Evidently the selective reaction 2 is unique to the IL environment.

In a typical procedure, a 22 ml Parr autoclave equipped with a magnetic stirrer was charged with 25 mg of 5% Pd/C (Sigma–Aldrich, 0.05 mmol) dispersed in 1.0 g of [bmim]BF_4, this IL was prepared according to the literature,[9]) 113.0 mg (1 mmol) of ethyl cyanoacetate, **2**, 15 mg EDDA (0.1 mmol) and 1 mmol of a ketone or aldehyde, **1**. The autoclave was purged three times with dihydrogen and a pressure of 300 kPa was maintained throughout the process. The autoclave was placed in a thermostatic oil bath for the desired time. After cooling, the reaction mixture was extracted four times with 3 ml portions of diethyl ether. Analysis and mass balance were accomplished using gas chromatography. The combined extracts were evaporated under vacuum and purified over a silica gel column using 20 ml of a 5:1 petroleum ether–ethyl acetate mixture as eluent. The products were identified using mass spectroscopy. The mass balance was calculated based on GC analysis using authentic samples as standards.

Both the Pd/C and EDDA catalysts remained in the ionic liquid after the extraction step with diethyl ether and were consequently recycled for a second catalytic sequence. The combined solvent and catalyst mixture could be used in five consecutive experiments without any loss in activity and selectivity. The prompt dispersion of the Pd/C catalyst in [bmim]PF_6 and its convenient reuse were previously reported by Hagiwara et al.[10] who applied this system to the Heck reaction.

With aliphatic linear aldehydes as substrates, the second reaction, took place swiftly at 25 °C. Thus acetaldehyde, propanal, butanal, pentanal, hexanal, and phenylacetaldehyde all reacted according to Eq. 2 with 100% conversion after 12 h with yields of the saturated products exceeding 90% in all cases (Table 1, entries 8–12).

Aromatic aldehydes required a higher temperature. At 95 °C complete conversion was recorded for benzaldehyde, 2-tolualdehyde, 4-anisaldehyde, 2,4-dimethoxybenzaldehyde, 2,3-dimethoxyacetaldehyde, 4-isopropylbenzaldehyde, 2-naphthaldehyde, 2-, 3- and 4-chlorobenzaldehyde after 4.5 h (Table 1, entries 1–7).

Table 1. Domino condensation and reduction results (Eq. 2)

Entry	Substrate	Time (h)	Yield (%) and conversion (%) (based on GC)
1[a]	Benzaldehyde	4.5	99(100)
2[a]	4-Anisaldehyde	4.5	85(100)
3[a]	2,4-Dimethoxybenzaldehyde	4.5	92(100)
4[a]	2,3-Dimethoxybenzaldehyde	4.5	90(100)
5[a]	4-Isopropylbenzaldehyde	4.5	100(100)
6[a]	2-Naphthaldehyde	4.5	71(100)
7[a]	4-Chlorobenzaldehyde	5	70(100)
8[a,c]	Propanal	12	92(100)
9[a,c]	Butanal	12	90(100)
10[a,c]	Pentanal	12	95(100)
11[a,c]	Hexanal	10	90(100)
12[a]	Phenylacetaldehyde	4.5	97(100)
13[a]	Acetophenone	4	85(30)
14[a]	Cyclohexanone	4	100(100)
15[b]	Ethyl acetoacetate	15	98(75)
16[b]	Diethyl malonate	17	27(50)
17[b]	Ethyl cyanoacetate	5	98(90)

[a] Ethyl cyanoacetate was used as substrate.

[b] 4-Anisaldehyde was used as substrate.

[c] The reaction was carried out at room temperature. Experimental procedure: see text.

The yield of the saturated aromatic products exceeded 95% in all cases with the exception of 2-naphthaldehyde (71% of the saturated product and 28% of the unsaturated product). This is probably due to steric hindrance affecting the hydrogenation rate (Table 1, entry 6). The reactions of chlorobenzaldehydes suffered from competing dehydrochlorination which decreased the yields of the desired product to 70% (Table 1, entry 7).

Ketones such as acetophenone and cyclohexanone reacted under the latter conditions to give complete conversion and practically quantitative yields of the saturated product (Table 1, entries 13–14).

Other active methylene compounds such as ethyl acetoacetate, diethyl malonate, and ethyl cyanoacetate reacted with aliphatic and aromatic aldehydes in a similar manner (Table 1, entries 15–17).

In view of a kinetic analysis of the second reaction with acetaldehyde as an electrophile (based on GC analyses of samples taken from the reaction mixture every 30 min), we asserted that the rate of the condensation step is approximately an order of magnitude faster than the hydrogenation step.

We verified that competing condensation reactions of the aldehydes with the weakly acidic IL solvent (an imidazole salt with a $pK_a = 24$) reported by Mereu and co-workers[11] did not occur under our reaction conditions.

Other supported noble metals such as Ru/C, Rh/C and Pt/C all gave poor hydrogenation performance in the second reaction under the above conditions.

To conclude, we have demonstrated that a Knoevenagel type condensation can be coupled effectively with catalytic hydrogenation in an ionic liquid as a solvent, to engender a tandem process directly leading to functional saturated carboxylic acids.

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