Rhodium catalysed coupling reaction of myrcene with ethyl acetoacetate in the ionic liquid 1-ethyl-3-methylimidazolium triflimide

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Abstract—The ionic liquid 1-ethyl-3-methylimidazolium triflimide was used successfully as the reaction medium to carry out the rhodium catalysed coupling of myrcene with the active methylene compound ethyl acetoacetate in the presence of TPPMS as the ligand. Coupling product was obtained in 93% isolated yield without any side product formation when a 1:50 ratio of rhodium catalyst/TPPMS was used.
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1. Introduction

Non-aqueous room temperature ionic liquids are of particular interest since they are increasingly considered as a new class of solvents, with a spectrum of physical and chemical properties much larger than that of organic or inorganic classical solvents. Also, they are becoming increasingly important as a non conventional, novel class of solvents for biphasic catalytic reactions[1–7] and outstandingly good solvents for a wide range of inorganic, organic and polymeric materials. One area where ionic liquids promise to make a large impact is in homogeneous catalysis, where the catalyst is typically dissolved in the solution along with the reactants. The solvent in homogeneous catalysis can influence the course of a reaction by increasing reaction rates and allowing optimisation of the control of the chemo, regio, stereo and enantioselectivities of the reaction. In transition metal based catalysis as well as in ionic catalysis, the solvent has to solubilize and stabilize the active species but not interact with the transition metal carbon bond of the intermediate and should not compete with the reactant for the metallic coordination center. The major disadvantage of using a solvent is the need to separate it from the catalyst and the products. This is why despite the benefits many homogeneous processes are carried out without solvent and the active species is dissolved in the reactants and products. Ionic liquids (ILs) with appropriate

counteranions can offer a highly polar but non-coordinating environment for the reaction unlike normal polar solvents like acetonitrile that coordinates with the metal complexes and therefore hinders the reaction.[8] Many organic[9–15] and organometallic[16–23] catalysed reactions were successfully carried out in ionic liquids.

Transition metal catalysed reaction of 1,3-diene with carbon nucleophiles is a well-known carbon–carbon bond forming reaction.[24] These reactions are catalysed by Rh,[25,26] Pd[27] or Ni[28] complexes. Generally, active methylene compounds are used as pronucleophiles in these reactions. The reaction of myrcene with ethyl acetoacetate as a carbon nucleophile yields a mixture of the alkylation products **3a** and **3b** (Scheme 1). The utility of these compounds as intermediates for the synthesis of vitamins A and E makes this reaction a most important one from an industrial point of view. Thus, Rhodia runs a process for the production of geranylacetone involving the alkylation of ethyl acetoacetate with myrcene catalysed by a water soluble Rh/TPPTS catalytic system. Two subsequent reaction steps convert geranyl acetone to vitamin E.[29]

We decided to explore the transition metal catalysed alkylation of ethyl acetoacetate with myrcene in the ionic liquid 1-ethyl-3-methylimidazolium triflimide ([emim][NTf$_2$]), with the following items in mind: first, finding a better reaction medium and catalytic system for carrying out this rhodium catalysed cross coupling reaction; second, recycling the catalytic system for several runs; third, controlling the side reaction, which normally occurs during the coupling reaction.

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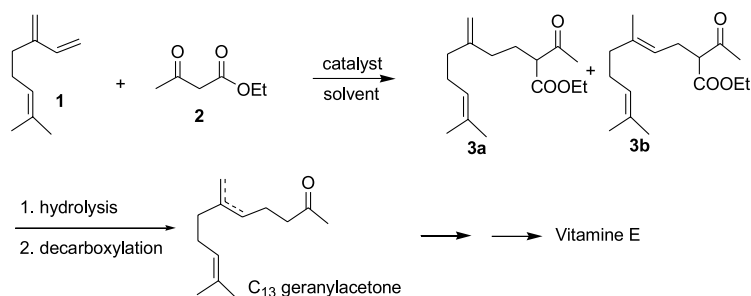
Scheme 1.

2. Results and discussion

2.1. Catalytic system for myrcene coupling

1-Ethyl-3-methylimidazolium triflimide, [emim][NTf$_2$] was chosen as the ionic liquid because of its non miscibility with water and low viscosity. Furthermore, it is easy to get analytically pure (see Section 4) and with low water content, e.g. below 50 ppm just by pumping under high vacuum at 60°C for 3 h. We have used different rhodium and palladium catalysts to carry out the alkylation reaction of ethyl acetoacetate as the pronucleophile with myrcene. A catalytic amount of sodium carbonate was used as the base for our preliminary studies. In all these reactions, ionic liquid and substrates formed a biphasic system. No added solvent was used for the reaction. Transition metal complex and ligand were dissolved in the ionic liquid forming a solution of the catalyst in the bottom layer while the reactants formed the top layer. Various catalysts and reaction conditions were tried and some are reported in Table 1.

When Wilkinson catalyst was used without any phosphine ligand, even after 24 h no coupling product was observed (entry 1). So in order to activate the catalytic system, a phosphite ligand i.e. P(OEt)$_3$ was used. It is known in the literature that Wilkinson catalyst forms active catalysts with phosphites, which are very efficient in carrying out allylic alkylation reactions.[30] Under these conditions, myrcene underwent complete conversion within 3 h. The product formed was not the coupling product but instead the product of self-condensation of myrcene. Our next choice of catalyst was [RhCl(COD)]$_2$ in the presence of triethylphosphite as ligand. Here the starting materials were recovered after 40 h. The expected coupling product was obtained in 30%

yield when triphenylphosphinemonosulphonate sodium salt (TPPMS) was used as the ligand with RhCl$_3$. But unfortunately the reaction was not complete even after 36 h. Further heating did not improve the conversion. A few palladium derivatives were also tried as catalyst. Palladium acetate in the presence of triphenylphosphine or palladacycle[31] obtained from palladium acetate and o-tolylphosphine were used. In both cases no coupling product was formed.

Since RhCl$_3$/TPPMS system gave the expected product in 30% yield, another rhodium catalyst precursor, [RhCl(COD)]$_2$ was tried in place of RhCl$_3$ in the presence of TPPMS as the ligand. The reaction was carried out using [emim][N(SO$_2$CF$_3$)$_2$] as a typical ionic liquid and sodium carbonate as the base. The coupling products were obtained as an isomeric mixture of **3a** and **3b** (**3a/3b**=1:1) in a very good isolated yield (93%) using 0.5% of [RhCl(COD)]$_2$ as the pre-catalyst. The reaction was very clean and no side products were observed.

In addition to this we also observed that the rate and the yield of the reaction changed by changing the catalyst/ligand ratio. The amount of ligand also played a major role in recycling the catalyst.

2.2. Variation of [RhCl(COD)]$_2$/TPPMS ratio

Variations of this ratio from 1:2 to 1:50 have been studied and results are reported in Table 2. When 2 equiv. of TPPMS were added to [RhCl(COD)]$_2$ no coupling was observed even after 2 days. With 5 equiv. of the ligand, 35% of coupling products **3** were obtained after 2 days of reaction, thus showing that this rhodium complex is a better catalyst precursor than RhCl$_3$. When the catalyst/ligand

Table 1. Variation of catalyst in the myrcene coupling with ethyl acetoacetate in [emim][NTf$_2$][a]

Entry	Transition metal complex (M)	Ligand (L)	M/L	Time (h)	Temperature (°C)	Yield[b] (%)
1	RhCl(PPh$_3$)$_3$	–	–	24	100	00
2	RhCl(PPh$_3$)$_3$	P(OEt)$_3$	1:5	3	100	00
3	[RhCl(COD)]$_2$	P(OEt)$_3$	1:5	40	90	00
4	RhCl$_3$	TPPMS[c]	1:5	36	90	30
5	Pd(OAC)$_2$	PPh$_3$	1:5	22	100	00
6	Palladacycle[d]	–	–	24	90	00

[a] 1 ml of IL for 0.0022 mmol of catalyst and 1.1 mmol of myrcene were used.
[b] Isolated yield.
[c] TPPMS=triphenylphosphinemonosulphonate sodium salt.
[d] Ref. 30.

Table 2. Alkylation of ethyl acetoacetate with myrcene: variation of the RhCl [COD]$_2$/TPPMS ratio at 90°C

No of runs	Catalyst:ligand	Time (h)	Yield (%)[a]	**3a/3b**
1	1:2	48	00	–
1	1:5	48	35	1:1.3
1	1:10	40	82	1:1.3
2	1:10	48	00	–
1	1:20	28	85	1:1.3
2	1:20	48	00	–
1	1:50	24	93	1:1.6
2	1:50	33	60	1:1.6
3	1:50	48	00	–

[a] Yield of isolated pure products.

ratio was changed to 1:10, then, the conversion of myrcene was 100% and the isolated yield was 82% with an *exo:endo* (**3a/3b**) ratio of 1:1.3. The product was extracted with pentane and the solution of catalyst in the ionic liquid was reused for a second run. The advantage of using TPPMS as the ligand is that the complex formed with this phosphine was not extracted with common organic solvents like pentane. Although not quantified, leaching of the complex should be very small since the organic layer from the extraction was colourless. So the complex could be recycled eventually without loss of activity. But unfortunately, in the second run no coupling product was observed. When the mixture was heated for long time myrcene underwent quantitative self-condensation. The analysis of this product by ^{1}H, ^{13}C and GC-MS showed that it is a dimer of myrcene with the molecular ion at m/z=272.

Considerable increase in the rate of the reaction was observed when 1:20 ratio was used. The reaction time was reduced from 48 h to 28 h. But the catalyst was not active for a second run. When the quantity of ligand used was increased to a large extent like 1:50, in addition to the reaction rate, the yield was also increased to 93%. Interestingly the catalyst was also active for the second run with an increased reaction time and a lower yield of 60%. In the third run again no coupling product was obtained but myrcene underwent self-condensation after 2 days of reaction. All the above observations show that the amount of phosphine plays a vital role in this reaction. This also implies that the phosphine was inactivated during each run. In order to get some insight into this phenomena, ^{31}P NMR of the complex were run before the reaction. TPPMS alone appeared as a singlet at $\delta=-4$ ppm. A doublet was observed at 27 ppm for the rhodium–phosphine complex in [emim][NTf$_2$]. After completion of the reaction, the ionic liquid solution of the catalyst showed a singlet at 32 ppm which was assigned to the TPPMS oxide. The oxidation of phosphine ligands in this reaction has been discussed[26a] and in our case may be due to the presence of some residual water in the reaction mixture. This would hamper the reuse of the phosphine.

2.3. Comparison with water

As we have seen above, the alkylation of ethyl acetoacetate with myrcene proceeded well at 70°C in the presence of 0.5% [RhCl(COD)]$_2$, 50 equiv. of TPPMS as the ligand and a catalytic amount of sodium carbonate as the base in

[emim][NTf$_2$]. It seems to us that it was of interest to perform the coupling reaction in water in order to compare the two systems. Therefore, the coupling reaction of myrcene was run under the same conditions as described above in a biphasic system containing the catalyst in the aqueous phase and the reactant in the second phase. This led to a 30% conversion after prolonged reaction time. This result is significantly different from those obtained in water at 90°C (100% conversion after 3.3 h in presence of 0.17% of [RhCl(COD)]$_2$ and a 1:42 rhodium catalyst/TPPMS ratio) as described in Ref. 26a. Although the reaction conditions are not exactly the same, the reasons for such a difference remains unclear.

From the above results it is clear that the coupling reaction in [emim][NTf$_2$] gave superior results with 100% conversion into the desired products and no by-products. It was also possible to reuse the same catalyst for a second run which gave a 60% isolated yield of **3a** and **3b**. Reuse for a third time did not give the desired product but the myrcene dimerisation product.

2.4. Use of TPPTS as the ligand

The triphenylphosphine trisulphonic acid sodium salt (TPPTS) was also tried as the ligand for the same reaction using identical conditions as in the case of TPPMS. The reaction was tried with the different catalyst/phosphine ratios, i.e. 1:10 and 1:50. TPPTS was added as a dried solid as well as a 33% water solution. In all the attempts the reaction failed. This may be because the phosphine did not dissolve in the ionic liquid.

2.5. Role of the base

It was shown earlier that the coupling reaction worked well with sodium carbonate. Under identical conditions to those used with TPPMS as the ligand, Bu$_4$NF, Et$_3$N and pyrrolidine were tried as bases. The starting materials were recovered in all cases thus showing that the choice of the base is also crucial in this coupling reaction.

3. Conclusions

[RhCl(COD)$_2$]/TPPMS was found to be a good catalytic system for the coupling reaction of myrcene with ethyl acetoacetate in the ionic liquid [emim][NTf$_2$]. The catalyst solution was reused one time for a 1:50 ratio of [RhCl(COD)]$_2$/TPPMS. The coupling reaction was a very clean process. No side products were observed and a 93% isolated yield of pure coupling product was obtained. Deactivation of the catalytic system preventing its recycling has been observed. The use of soluble bases such as Bu$_4$NF, Et$_3$N or pyrrolidine inhibited the reaction.

4. Experimental

4.1. General information

All reactions were carried out under argon atmosphere using Schlenk tubes and vacuum line techniques [emim][NTf$_2$][32]

was prepared according to a literature procedure and dried under high vacuum for several hours at 60°C. TPPTS was obtained from Rhodia.

^{1}H and ^{13}CNMR spectra were recorded on Bruker ARX200 Spectrometer (200 MHz for proton, 50 MHz for carbon) or Bruker AM 300 WB Spectrometer (300 MHz for proton, 75 MHz for carbon and 121.49 MHz for phosphorous). Chemical shifts are expressed in ppm downfield from TMS and phosphorous with respect to H_3PO_4. IR spectra were recorded on a BIO-RAD FTS 175C FT-IR Spectrometer. Mass spectra were measured on a Varian MAT 311 Spectrometer (CRMPO, University of Rennes, France).

4.1.1. Procedure for the preparation of [emim][NTf$_2$].[32]
Aqueous solutions of 1-ethyl-3-methylimidazolium bromide (10 g, 0.05 mol in 30 ml of distilled water) and lithio trifluoromethane-sulfonimide (14.4 g, 0.05 mol in 30 ml of distilled water) were mixed and shaken in a 100 ml separating funnel. After decantation, the lower layer was collected and washed several times with 20 ml portions of distilled water until the silver nitrate test became negative (4 to 5 times). The [emim][NTf$_2$] was dried under high vacuum at 60°C to give a colourless liquid (18 g, 90%) containing less than 50 ppm of water as measured by Karl–Fisher technique. Anal. calcd for $C_8H_{11}F_6N_3S_2O_4$: C 24.55, H 2.81, F 29.16, N 10.74. Found: C 24.72, H 3.01, F 28.95, N 10.58.

4.1.2. General procedure for the coupling reaction of myrcene.
1 g of [emim][N(SO$_2$CF$_3$)$_2$] was taken in a Schlenk tube containing a small stirring bar. To the ionic liquid, 0.05 g (0.11 mmol of TPPMS) and [RhCl(COD)]$_2$ (1 mg, 0.0022 mmol) were added to give a pale yellow coloured heterogeneous solution. The mixture was heated to 70°C followed by the addition of Na$_2$CO$_3$ (0.01 g, 0.11 mmol) to give a clear yellow solution. Myrcene (0.15 g, 1.1 mmol) was added to give two clear layers. After heating the mixture at 90°C for 20 min, ethyl acetoacetate (0.22 g, 1.7 mmol) was added. The reaction was allowed to proceed at 90°C. The progress of the reaction was monitored by ^{1}H NMR. After completion of the reaction (24 h), the product was extracted several times with dry pentane. Solvent was removed under vacuum to give a pale yellow liquid as the product. The crude product was purified by kügelrohr distillation (oven temperature: 50°C, 0.01 Torr) to give 0.29 g of a 1:1.6 mixture of **3a** and **3b**[25,26] as a clear oil (93% yield). ^{1}H NMR, (200 MHz, CDCl$_3$, δ): 1.19 (t, J=7.0 Hz, CH$_3$), 1.20 (t, J=7.3 Hz, CH$_3$), 1.51 (s, CH$_3$), 1.53 (s, CH$_3$), 1.55 (s, CH$_3$), 1.60 (s, CH$_3$), 1.93 (m, CH$_2$), 2.14 (s, CH$_3$), 2.15 (s, CH$_3$), 2.47 (dd, J=7.3 Hz, CH$_2$), 3.36 (t, J=7.3 Hz, CH), 4.10 (q, J=7.0 Hz, CH$_2$), 4.12 (q, J=7.3 Hz, CH$_2$), 4.68 (d, J=7.3 Hz, CH$_2$), 4.98 (m, CH). ^{13}C NMR, (50 MHz, CDCl$_3$, δ): 14.46, 16.43, 18.04, 26.01, 26.45, 26.68, 26.73, 26.86, 27.27, 29.31, 29.44, 34.00, 36.05, 40.02, 59.42, 60.17, 61.61, 110.60, 120.08, 124.27, 131.83, 132.06, 138.68, 148.32, 169.93, 170.11, 203.37.

4.2. Recycling of the catalyst

After extraction of the product from the ionic liquid in the first run, the catalyst solution in the ionic liquid was left under vacuum (0.01 Torr) for 1 h at room temperature. To

this the same quantity of the starting materials was then added under argon and the reaction run as given above.

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