

The Effect of the Catalyst on the Selectivity of the Heterogeneous 1,4-addition of Organomagnesium Compounds to Chalcone

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Received: 21 February 2019, Accepted: 15 May 2019, Published online: 27 June 2019

Abstract

The conjugate addition in the presence of a catalytic amount of copper is a widely used method for the formation of a C-C bond. However, mostly homogeneous catalysts and/or homogeneous ligands are used in these type of reactions. Previously we reported the heterogeneous catalytic 1,4-addition of organomagnesium compounds to chalcones in the presence of Cu(II) on 4Å molecular sieve support. In this study various heterogeneous supported catalysts were tested in the 1,4-addition reaction, such as La(III), Ti(IV), In(III), Co(II) and Ni(II) on 4Å molecular sieve support. Using the Ti(IV)-4A the desired products could be obtained in excellent yields and no 1,2-addition by-product could be detected. Therefore the reusability of the catalyst was tested in a second reaction. It was found, that the Ti(IV)-4A cannot be reused in this type of reaction, due to significant loss of selectivity. In the second experiment a considerable amount of the 1,2-addition product was formed. Thus, the Cu(II)-4A is a suitable catalyst for the heterogeneous 1,4-addition of organomagnesium compounds to chalcones, as described in our previous work.

Keywords

heterogeneous catalysis, copper, 1,4-addition, chalcone, organomagnesium compounds

1 Introduction

The formation of a C-C bond is a widely researched field of interest in synthetic organic chemistry. One of the most important methods to form a C-C bond is the addition of nucleophiles to electron-deficient conjugated structures. Usually, in the reaction of α,β -unsaturated carbonyl compounds and organometallic reagents a 1,2-addition occurs. However, in the presence of a catalytic amount of a copper salt 1,4-addition was observed [1-4].

Kharash and Tawney [5] achieved a conjugate addition in the reaction of methylmagnesium bromide and isophorone by adding a catalytic amount of copper chloride to the reaction mixture. In the past few years the reaction was thoroughly examined and a reactivity order of the organometallic reagents was set. Accordingly, the organomagnesium reagents are most likely to react in this kind of reactions [5].

Since the first attempt the transition metal catalysed 1,4-addition was examined thoroughly. In several cases the stereochemistry of the reaction was investigated in the presence of various catalyst ligands [6-8].

There are several articles in the literature, in which 1,4-addition reactions have been carried out in the presence of various metal salts. Pérez et al. [9] reported a nickel-catalysed 1,4-addition reaction of triorganotin compounds to α,β -unsaturated systems. The reactivity of several nickel complexes was investigated and the Ni(COD)₂ complex was found to give the best results. The 1,4-addition products were obtained in a yield of 80 % [9].

An Italian research group investigated the conjugate addition of indoles and thiols to α,β -unsaturated ketones, using indium(III) bromide as catalyst. Followed by a 1,2-addition of trimethylsilylcyanide they were able to prepare the corresponding β -indolyl-ketones, which can be interesting building blocks of biologically active compounds and natural products [10].

On the other hand, Kelly and Gilheany [11] found, that in the conjugate addition of organomagnesium reagents to α,β -unsaturated carbonyl compounds InCl₃ promoted the 1,2-addition. The reaction was carried out using multiple

carbonyl compounds, and in some cases the 1,2-addition product could be obtained selectively [11].

However, the major problem of these reactions is that they use homogeneous catalysis and/or homogeneous ligands. After the reaction the separation of these catalysts and ligands from the reaction mixture can be tedious. The separation of a heterogeneous catalyst is generally easier, thus we examined the conjugate addition using heterogeneous catalysts.

2 Results and discussion

Recently, we reported a heterogeneous catalytic method for the addition of organomagnesium compounds to chalcones in the presence of copper(II) on 4 Å molecular sieve support [Cu(II)-4A]. The reaction afforded the desired products in good yields and no by-product could be observed [12].

In continuation of our interest we examined the reaction of ethylmagnesium iodide (**2**) and chalcone (**1**) in the presence of various heterogeneous catalysts. We aimed to investigate the effect of the applied catalysts on the selectivity of the 1,4-addition. Different metals [La(III), Ti(IV), In(III), Co(II), Ni(II)] on 4 Å molecular sieves were used as catalysts. The results are summarized in Table 1. The efficiency of the non-impregnated molecular sieves was also tested. In all cases the 1,4-addition product (**3**) was the major product and the 1,2-addition product could not be detected. However, in the case of the In(III)-, Co(II)- and Ni(II)-4A catalysts another by-product (**4**) was observed in the GC-MS spectra of the crude products (Fig. 1). This can be formed in the reaction of the desired product (**3**) with another chalcone molecule (**1**) in an aldol-type reaction. When the La(III)-4A catalyst was used, no by-product could be observed on the ¹H NMR and GC-MS spectra, but the yield remained significantly lower, than in the cases of the Cu(II)- and Ti(IV)-4A catalysts.

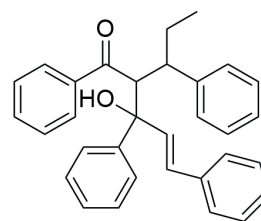
Besides the already reported Cu(II)-4A, the Ti(IV)-4A appeared to be efficient in the conjugate addition reaction. The desired product (**3**) could be obtained with a yield of 80 % in both reactions. Therefore the reaction of phenylmagnesium iodide (**5**) with chalcone was also examined in the presence of Ti(IV)-4A and the desired conjugate addition product (**6**) was obtained in excellent yield. The results are presented in Table 2. Using Ti(IV)-4A as the catalyst, in the reaction of phenylmagnesium iodide (**5**) and chalcone (**1**) the 1,4-addition product (**6**) was obtained in a yield of 90 %. Therefore it seems, that the Ti(IV)-4A is also a suitable catalyst for the conjugate addition of arylmagnesium halides.

Table 1 Reaction of ethylmagnesium iodide (**2**) with chalcone (**1**) in the presence of various catalysts

Entry	Catalyst	Yield ^a (%)
1.	Cu(II)-4A	80
2.	La(III)-4A	67
3.	Ti(IV)-4A	80
4.	In(III)-4A	80
5.	Co(II)-4A	70
6.	Ni(II)-4A	75

2 mmol magnesium, 2.3 mmol ethyl iodide, 1 mmol chalcone, 0.1 g catalyst, 9 mL diethyl ether, reflux temperature, 6 h

^a Isolated yield, the purity is checked by GC-MS



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Fig. 1 The by-product identified by GC-MS

Table 2 Examination of the applicability of the Ti(IV)-4A catalyst in the reaction of various organomagnesium halides (**2** or **5**) with chalcone (**1**)

Entry	R-MgX	Yield with Cu(II)-4A (%) ^a	Yield with Ti(IV)-4A (%) ^a
1.	MgI	80	80
2.	MgI	83	90

2 mmol magnesium, 2.3 mmol alkyl/aryl halide, 1 mmol chalcone, 0.1 g catalyst, 9 mL diethyl ether, reflux temperature, 6 h

^a Based on GC-MS

In order to demonstrate the need for the metal catalysis, the reaction was carried out in the presence of pure 4 Å molecular sieves. Based on the GC-MS spectra it can be concluded, that the desired product (**3**) was formed in the reaction with high yield, but the ¹H NMR spectrum showed the presence of several by-products, which were not formed in the metal catalysed reactions. These by-products could not be separated from the product.

After the thorough investigation of the effect of the catalyst on the 1,4-addition reaction we wished to examine the recyclability and reusability of the catalyst. In our previous report the reusability of the Cu(II)-4A was described [12]. Besides the Cu(II)-4A the Ti(IV)-4A was found to be an efficient catalyst in the conjugate addition

of organomagnesium halides to chalcone (**1**). Therefore, the reusability of the Ti(IV)-4A was tested in the reaction of ethylmagnesium iodide (**2**) with chalcone (**1**). After the completion of the reaction the catalyst was filtered from the reaction mixture, washed with acetone and dried at 120 °C for 1 h. Then it was used in a second experiment. On the ¹H NMR spectrum of the crude product several by-products could be detected, which were not formed in the first reaction. In the second reaction with the Ti(IV)-4A a significant amount of the 1,2-addition product was formed as well. Therefore it can be concluded, that the Ti(IV)-4A catalyst cannot be reused in the heterogeneous catalytic conjugate addition reaction (Table 3).

The products were subjected to an XRF analysis to check the leaching of the metals from the surface of the catalysts. In accord with the results obtained earlier [13], no appreciable amount of metal could be detected. This means that the leaching of the metal during the reaction is negligible.

3 Experimental

3.1 General methods

GC–MS measurements were performed on an Agilent 6890N-GC-5973N-MSD chromatograph, using a 30 m × 0.25 mm Restek, Rtx-5SILMS column with a film layer of 0.25 μm. The initial temperature of column was 45 °C for 1 min, followed by programming at 10 °C/min up to 310 °C and a final period at 310 °C (isothermal) for 17 min. The temperature of the injector was 250 °C. The carrier gas was He and the operation mode was splitless. ¹H NMR spectra were made on BRUKER Avance-300 instrument using TMS as an internal standard in CDCl₃.

All reagents and solvents were purchased from Merck Hungary Ltd.

3.2 Preparation and characterization of the catalysts

A suspension of 4 Å molecular sieves (2 g) in deionized water (200 mL) containing 2 mmol of the metal salt (CuCl₂·2H₂O, La(NO₃)₃·6H₂O, TiCl₄, In(NO₃)₃·H₂O, CoCl₂·6H₂O, NiCl₂·6H₂O) was stirred for 12 h at room temperature. The solid was filtered, washed with deionized water (50 mL) and acetone (20 mL), then dried in an oven at 120 °C for 1 h. The metal content was determined by ICP-OES (see Table 4). The original surface area of the molecular sieves (810 m²/g) dropped after the impregnation. During the impregnation metal ions can replace the sodium ions in the synthetic microporous sodium aluminosilicate. Energy-Dispersive X-ray Spectroscopy (EDS) showed that metals evenly covered the support's surface.

Table 3 Investigation of the reusability of the catalysts

Number of uses	Yield (%)	
	Cu(II)-4A	Ti(IV)-4A
1	80	80
2	79	60

Table 4 Characterization of the catalysts

Entry	Catalyst	Metal content (wt%)	Surface area (m ² /g)
1.	Cu(II)-4A	5.80	360
2.	La(III)-4A	3.88	35
3.	Ti(IV)-4A	3.99	122
4.	In(III)-4A	10.20	30
5.	Co(II)-4A	4.98	270
6.	Ni(II)-4A	n.d. ^a	n.d. ^a

^aNot determined

Surface analysis by scanning electron microscope (SEM) showed that the zeolite crystals retained their cubic form.

3.3 General procedure for the preparation of compounds **3** and **6**

Compounds **3** and **6** were synthesized according to our previous report [10]. To the mixture of magnesium (0.05 g, 2 mmol) and 3 mL of diethyl ether the solution of the corresponding halide (2.3 mmol) in diethyl ether (3 mL) was added. After the formation of the corresponding Grignard-reagent (**2** or **5**) the catalyst was added. Then the solution of the chalcone (0.21 g, 1 mmol) in diethyl ether was added dropwise. The reaction mixture was stirred for 6 h at 35 °C, then quenched with water. The catalyst was filtered off and washed with diethyl ether. The layers were separated and the aqueous layer was washed with diethyl ether. The combined organic phase was dried over anhydrous sodium sulfate and the solvent was evaporated. The crude product was examined by ¹H NMR and GC-MS.

1,3-diphenyl-1-pentanone (**3**) [14]: ¹H NMR (300 MHz, CDCl₃) δ = 0.80 (t, 3H); 1.58-1.87 (m, 2H); 3.20-3.32 (m, 3H); 7.12-7.57 (m, 8H); 7.90 (d, 2H).

1,3,3-triphenyl-1-propanone (**6**) [15]: ¹H NMR (300 MHz, CDCl₃) δ = 3.79 (d, 2H); 4.89 (t, 1H); 7.18-7.69 (m, 13H); 7.99 (d, 2H).

3.4 The reusability of the Ti(IV)-4A catalyst

The catalyst used in a previous reaction was washed with acetone and dried at 120 °C for 1 h. Then the catalyst was used in another reaction of ethylmagnesium iodide (**2**) and chalcone (**1**). The reaction was carried out according to *General procedure*.

4 Conclusion

Besides Cu(II)-4A Ti(IV)-4A was also found to be an efficient heterogeneous catalyst in the conjugate addition reaction of organomagnesium halides to chalcone. The

desired 1,4-addition products were obtained in high yields after a simple workup of the reaction mixture. However the Ti(IV)-4A catalyst cannot be reused in the reaction due to loss of selectivity towards the 1,4-addition product.

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