Letter

Coupling reactions between acyl chlorides and Grignard reagents in the presence of a supported Fe(III)-complex

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Abstract

The polymer-supported Fe(III) complex obtained by copolymerization of $Fe(AAEMA)_3$ [$AAEMA^-$ = deprotonated form of 2-(acetoacetoxy) ethyl methacrylate] with suitable acrylamides facilitates the coupling reaction between acyl chlorides and Grignard reagents, affording ketones with yields up to 96%. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

The metal-catalysed cross-coupling reaction between an organometallic reagent and an organic halide is a widely used method for the formation of new carbon–carbon bonds [1,2]. Recent examples of such couplings count the reaction between triflates and alkyl cuprates in the presence of catalytic amount of copper(I) halides [3], the reaction between unsaturated alkyl bromides and diethylzinc in the presence of $Ni(acac)_2$/LiI [4] and the reaction between Grignard reagents and alkyl bromides in the presence of

catalytic amount of $Li\{MnCl_2[C_6H_3(CH_2NMe_2)_2-2,6]\}$ [5]. However, while the use of soluble complexes to promote this reaction is well established, homogeneous catalysts are generally connected with problems of separation, recovery and regeneration of the catalysts.

To the best of our knowledge, the reported attempts to run coupling reactions with a heterogeneous catalyst are represented by the use of Pd(II) complexes anchored onto zeolites [6], glass beads [7] or molecular sieves [8] as catalysts for the Heck reactions between aryl halides and olefins, or the coupling reaction of substituted chlorobenzene leading to biphenyls catalysed by coal-supported palladium [9].

In the last years, we have studied the catalytic activity of new materials obtained by thermal

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copolymerization of complexes of general formula $M(AAEMA)_n$ (M = Fe, n = 3; M = Ni, Co, Pd, n = 2; $AAEMA^-$ = deprotonated form of 2-(acetoacetoxy) ethyl methacrylate) with N,N-dimethylacrylamide as comonomer, and N,N'-methylenebisacrylamide as cross-linker. These materials proved to be interesting heterogeneous analogues of dioxygenato (typically acetylacetonato) soluble complexes of Ni(II), Fe(III), Co(II) and Pd(II) for several organic reactions, including oxidations [10–14], Michael addition [15] and hydrogenation reactions [16].

In this paper we report on the catalytic activity of a polymer-supported Fe(III) catalyst as a heterogeneous analogue of $Fe(acac)_3$ that was found to be an active homogeneous catalyst for the synthesis of ketones starting from an acyl chloride and a Grignard reagent [17].

2. Results and discussion

The protocol common to all reactions was extremely simple and consisted of the addition of a Grignard reagent to a solution of an acyl chloride in THF at room temperature, over half an hour time, causing in each case the complete conversion of the acyl chloride.

In order to check and compare the activity of the β-ketoesterate complex $Fe(AAEMA)_3$ with that of the β-diketonato $Fe(acac)_3$, we used both complexes as catalysts for the coupling reaction of hexanoyl chloride with butyl magnesium chloride. Using $Fe(AAEMA)_3$ resulted in the obtainment of 96% yield in decan-5-one, a result comparable with that obtained using $Fe(acac)_3$ (97%). This finding encouraged us to test the efficiency of the copolymer of $Fe(AAEMA)_3$ (in the following Fe-pol), a heterogeneous analogue of $Fe(acac)_3$ as a supported catalyst for the coupling reaction of hexanoyl or benzoyl chloride with several Grignard reagents, according to Scheme 1.

Table 1 collects the scope of the investigated catalytic reactions.

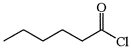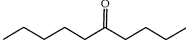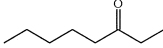The tests carried out on each reported reaction in the absence of a metal catalyst showed that in all
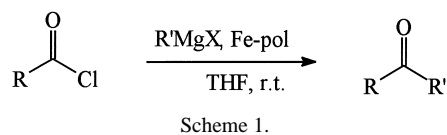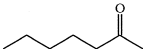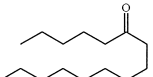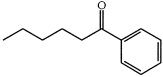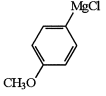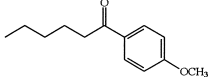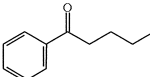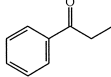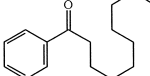

Scheme 1.

cases the yields toward ketones ranged between 5% and 30%: the formation of several by-products such as secondary and tertiary alcohols was observed. When the reaction between hexanoyl chloride and butyl magnesium chloride was carried out in the presence of the supported Fe(III) catalyst, a result comparable with those obtained in homogeneous phase (96% isolated yield in decan-5-one, entry **1**) was obtained. Elemental analysis carried out on the recovered resin revealed that the residual metal content was 91% with respect to the initially present metal loading (4.88% vs. 5.36% w/w). When recycled, the resin showed comparable activity and selectivity with respect to the first cycle (94% yield in decan-5-one, entry **2**). Good yields in ketones were also obtained in the reactions between hexanoyl chloride and ethyl magnesium bromide (91% yield in octan-3-one, entry **3**) or methyl magnesium chloride (84% yield in heptan-2-one, entry **4**). The yield in ketone was considerably lesser when nonyl magnesium bromide was used (isolated yield in pentadecan-6-one: 61%, entry **5**).

The coupling of aromatic Grignard reagents such as phenyl magnesium chloride or *p*-methoxy-phenyl magnesium chloride with hexanoyl chloride resulted in the synthesis of hexanophenone and *p*-methoxy-hexanophenone with yields as high as 71% (entry **6**), and 60% (entry **7**, isolated yield).

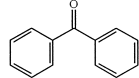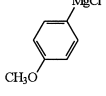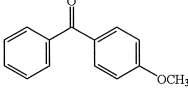The yield in decanophenone obtained using benzoyl chloride and nonyl magnesium bromide was 42% (entry **11**). Higher yields were obtained with short-chained Grignard reagents: 57% yield in butyl-phenylketone (entry **8**), 67% in ethyl-phenylketone (entry **9**) and 86% in acetophenone (entry **10**). When phenyl magnesium bromide was reacted with benzoyl chloride, a good yield in benzophenone (79%, entry **12**) was obtained, whereas *p*-methoxyphenyl magnesium chloride reacted with benzoyl chloride under the reported catalytic conditions, yielding 52% in *p*-methoxy-benzophenone (entry **13**).

Table 1
Synthesis of ketones

Entry	Acyl chloride	Grignard reagent	Ketones	Yield in ketones(%)[a]
1	(pentanoyl chloride structure)	$CH_3(CH_2)_3MgCl$	(ketone structure)	98 (96)
2[b]	"	"	"	94
3	"	CH_3CH_2MgBr	(ketone structure)	91
4	"	CH_3MgCl	(ketone structure)	84
5	"	$CH_3(CH_2)_8MgBr$	(ketone structure)	65(61)
6	"	(phenyl MgCl structure)	(ketone structure)	71
7	"	(4-methoxyphenyl MgCl structure)	(ketone structure)	63(60)
8	(benzoyl chloride structure)	$CH_3(CH_2)_3MgCl$	(ketone structure)	57
9	"	CH_3CH_2MgBr	(ketone structure)	67
10	"	CH_3MgCl	(ketone structure)	86
11	"	$CH_3(CH_2)_8MgBr$	(ketone structure)	42
12	"	(phenyl MgCl structure)	(ketone structure)	79
13	"	(4-methoxyphenyl MgCl structure)	(ketone structure)	52

All reactions were performed on 1.2 mmol scale; the conversion of the starting acyl halide was quantitative. The molar ratio between the Grignard reagent and the acyl chloride was 1:1 and the molar ratio between the acyl chloride and the supported metal was 33.3:1.

[a] Yields were determined by GLC; the yields of isolated purified products are shown in parentheses.

[b] Recycle of the previous run.

From the reported data it can be concluded that the copolymer of $Fe(AAEMA)_3$ represents one of the few examples of heterogeneous catalysts for C–C bond formation reactions: it was found responsible for the enhanced selectivity toward ketones in the coupling reactions between acyl chlorides and

Grignard reagents, the best results being obtained with aliphatic acyl chloride and short-chained alkyl magnesium halide.

3. Experimental

Chromatographic analyses were carried out on a Hewlett Packard 6890 instrument using an HP-5 phenyl-methyl-siloxane capillary column (30.0 m × 0.32 mm × 0.25 μm). GCMS data (EI, 70 eV) were acquired on an HP 5973 instrument. Conversions and yields were calculated by GLC analyses as moles of ketone per mole of starting substrate by using the internal standard method. THF was distilled, dried and stored under N_2 on metal sodium.

Hexanoyl chloride and benzoyl chloride were purchased from Aldrich and distilled prior to use. Grignard reagents were prepared in THF from the corresponding chlorides or bromides and titrated immediately prior to use. The supported Fe(III) catalyst was synthesised by thermal copolymerization of Fe(AAEMA)$_3$ [AAEMA$^-$ = deprotonated form of 2-(acetoacetoxy) ethyl methacrilate] with N,N-dimethylacrylamide, and N,N'-methylenebisacrylamide, according to Ref. [10] and contained 5.36% w/w of Fe.

In the case of 2-heptanone, benzophenone, 4-methoxybenzophenone, propiophenone, hexanophenone, decanophenone, 3-octanone, valerophenone and acetophenone, the products were identified by comparison of their MS spectra and retention times in GLC analyses with those of commercially available samples. 1-(4-Methoxyphenyl)-hexan-1-one and decan-5-one were isolated from the reaction medium by silica gel chromatography [eluants used for 1-(4-methoxyphenyl)-hexan-1-one: petroleum ether/ethyl acetate 10:1; for decan-5-one: petroleum ether/ethyl acetate 40:1], and characterised by comparison of their spectroscopic features with those respectively reported in literature [18–22]. Pentadecan-6-one was purified by silica gel chromatography (eluants: petroleum ether/ethyl acetate 40:1) and characterised on the basis of the following spectroscopic features.

Pentadecan-6-one: white needles, m.p.: 31.9–32.9, (lit. 32.5–33 [22]), IR (cm^{-1}): 2959 (s), 2930 (vs), 2858 (s), 1714 (s), 1411 (m), 1376 (w), 1243 (w), 1131 (w), 721 (w). ^{1}H NMR (CDCl$_3$) ppm: $\delta = 2.36$ (pt, 4H, C$^5H_2$, C$^7H_2$), $\delta = 1.54$ (m, 4H, C$^4H_2$, C$^8H_2$), $\delta = 1.26$ (m, 16 H), $\delta = 0.86$ (m, 6H, C$^1H_3$, C$^{15}H_3$). ^{13}C NMR (CDCl$_3$): 11.28, 11.29, 13.91, 14.09, 22.45, 22.65, 23.56, 23.89, 29.26, 29.41, 31.43, 31.65, 42.76, 42.82, 211.8 (C=O). MS [m/z, (I_{rel}%)]: 41 (22), 43 (46), 58 (42), 71 (88), 85 (34), 99 (74), 114 (27), 115 (27), 127 (34), 155 (100), 170 (17), 183 (15), 226 (8, M$^+$).

3.1. General procedure for the coupling reactions

The whole procedure was carried out under nitrogen. A three-necked flask, equipped with a dropping funnel and a Torion™ stopcock, was charged with the acyl chloride (1.2 mmol), the Fe(III) complex [Fe(acac)$_3$, Fe(AAEMA)$_3$, or the supported iron polymer, in all cases Fe/acyl chloride = 1/33.3 mol/mol] and the internal standard (biphenyl, 60 mg) in 12 ml of anhydrous THF and kept under vigorous stirring. The relevant Grignard reagent (1.2 mmol in 2.0 ml of THF) was added dropwise to the solution over a 20-min time. The reaction mixture was kept under stirring for further 5 min at room temperature and then analysed.

In order to perform a recycle, the catalyst was recovered by centrifugation, washed with THF (3 × 5 ml), water (5 ml), EtOH (3 × 5 ml) and Et$_2$O (3 × 5 ml) and dried under high vacuum.

References

[1] F. Diederich, P.J. Stang, Metal-Catalyzed Cross-Coupling Reactions, Wiley-VCH, Weinheim, 1998.
[2] K.C. Nicolau, E.J. Corenses, Classics in Total Synthesis, VCH, Weinheim, 1996, pp. 565–631.
[3] A. Sofia, E. Karlström, M. Rönn, A. Thorarensen, J.E. Bäckvall, J. Org. Chem. 63 (1998) 2517.
[4] R. Giovannini, T. Stüdemann, A. Devasagayaraj, G. Dussin, P. Knochel, J. Org. Chem. 64 (1999) 3544.
[5] J.G. Donkervoort, J.L. Vicario, J.T.B.H. Jastrezebski, R.A. Gossage, G. Cahiez, G. van Koten, J. Organomet. Chem. 558 (1998) 61.
[6] L. Djakovitch, H. Heise, K. Kohler, J. Organomet. Chem. 584 (1999) 16, and references therein.
[7] L. Tonks, M.S. Anson, K. Hellgardt, A.R. Mirza, D.F. Thompson, J.M.J. Williams, Tetrahedron Lett. 38 (24) (1997) 4319.
[8] C.P. Mehnert, D.W. Weaver, J.Y. Ying, J. Am. Chem. Soc. 120 (1998) 12289.

[9] S. Mukhopadhyay, G. Rothenberg, D. Gitis, H. Wiener, Y. Sasson, J. Chem. Soc., Perkin Trans. 2 11 (1999) 2481.

[10] M.M. Dell'Anna, P. Mastrorilli, C.F. Nobile, G.P. Suranna, J. Mol. Catal. 103 (1995) 17.

[11] M.M. Dell'Anna, P. Mastrorilli, C.F. Nobile, J. Mol. Catal. 108 (1996) 57.

[12] M.M. Dell'Anna, P. Mastrorilli, C.F. Nobile, J. Mol. Catal. 111 (1996) 33.

[13] M.M. Dell'Anna, P. Mastrorilli, C.F. Nobile, J. Mol. Catal. 130 (1998) 65.

[14] M.M. Dell'Anna, P. Mastrorilli, C.F. Nobile, M.R. Taurino, V. Calò, A. Nacci, J. Mol. Catal. 151 (2000) 61.

[15] P. Mastrorilli, C.F. Nobile, G.P. Suranna, J. Mol. Catal. 103 (1995) 23.

[16] M.M. Dell'Anna, M. Gagliardi, P. Mastrorilli, G. P. Suranna, C. F. Nobile, J. Mol. Catal. A, 256.

[17] V. Fiandanese, G. Marchese, V. Martina, L. Ronzini, Tetrahedron Lett. 25 (1984) 4805.

[18] P.S. Manchand, A. Schwartz, S. Wolff, P. Madan, Heterocycles 35 (1993) 1351.

[19] K. Suzuki, H. Kitagawa, T. Mukaiyama, Bull. Chem. Soc. Jpn. 66 (1993) 3279.

[20] H.G. Richey, W.F. Erickson, J. Org. Chem. 48 (1983) 4349.

[21] M.W. Anderson, R.C.F. Raymond, J. Saunders, J. Chem. Soc., Perkin Trans. 1 (1986) 1995.

[22] R.V. Koslenkowa, V.V. Kamzolkin, A.N. Bashkirov, Neftekhimiya 10 (1970) 707.