Journal of Organometallic Chemistry 624 (2001) 131–135

www.elsevier.nl/locate/jorganchem

Iron catalyzed hydrodebromination of 2-aryl-1,1-dibromo-1-alkenes

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Received 3 October 2000; accepted 6 December 2000

Dedicated with a deep respect and admiration to Professor J. Normant on the occasion of his 65th birthday

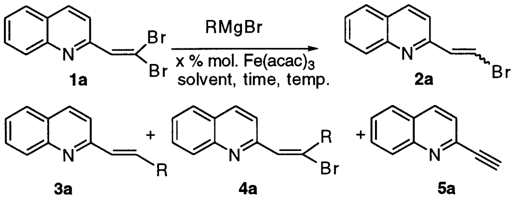
Abstract

2-Aryl- or 2-heteroaryl-1,1-dibromo-1-alkenes are reduced by Grignard reagents in a THF + NMP mixture in the presence of a catalytic amount of iron salts, to afford the corresponding *E* vinyl bromides. Further application to the one pot reduction-cross coupling reaction with Grignard reagents is highlighted. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Hydrodebromination; Grignard reagents; *E* vinyl bromides

1. Introduction

Only three examples of hydrodebromination of 1,1-dibromo-1-alkenes, to our knowledge, were reported in the literature [1]. These methods suffer from two major drawbacks; either the corresponding 1-bromo-1-alkene is obtained as a *Z*- and *E*-isomer mixture, and/or toxic *n*-Bu_3SnH is used in the presence of palladium catalyst. However, Cahiez and coworkers reported two interesting papers in which they described the reduction of 1-bromo-1-alkenes with Grignard reagents in high yields when the reaction is performed in the presence of manganese(II) halide [2], and in some particular cases, albeit in moderate yields, in the presence of $Fe(acac)_3$ [3a]. We were thus interested to check if the use of Grignard reagents, in the presence of transition metals such as Fe, Co, could advantageously perform the hydrodebromination of 1,1-dibromo-1-alkenes, and report herein our preliminary findings in this area (Scheme 1).



Scheme 1.

2. Results and discussion

We first used 1,1-dibromo-2-(2-quinolyl)-1-ethene (**1a**) as starting material, and studied the reaction conditions (Scheme 1 and Table 1). When **1a** was treated with 1.1 equivalents of *i*-PrMgCl in the presence of 5% molar of $Fe(acac)_3$ in a THF + NMP (1:1) mixture between − 10 and 0°C for 3 h, we were relatively surprised to find out that the desired compound **2a** was obtained in high yield as the sole *E*-isomer ($E > 95\%$ by ^{1}H-NMR on the crude mixture). Then we noticed that after only 30 min of reaction, the 1-bromo-1-alkene (**2a**) was obtained with identical high yield (84%). Compound **4a**, which could arise from a mono-coupling reaction of the Grignard reagent with **1a**, was not isolated, neither alkyne **5a** resulting from debromohydration. However, in the absence of either $Fe(acac)_3$ or NMP, no reaction occurred and the starting material was recovered unchanged. At low temperature no reaction was observed (− 78°C, entry 2). Lowering the catalyst loading to 1 mol% gave lower yields of the

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PII: S0022-328X(00)00934-7

Table 1
Hydrodebromination of 1,1-dibromo-2-(2-quinolyl)-1-ethene (**1a**) by Grignard reagents in the presence of transition metals in THF, for 30 min

Entry	R [a]	Catalyst [b]	*T* (°C)	Cosolvent [c]	Products [d] (yield)
1	*i*-Pr	Fe (5)	−10–0	NMP	**2a** (84)
2	*i*-Pr	Fe (5)	−78	NMP	NR
3	*i*-Pr	Fe (5)	−10–0	None	NR
4	*i*-Pr	None	−10–0	NMP	NR
5	*i*-Pr	Fe (1)	−10–0	NMP	**2a** (49)
6	*n*-Dodec	Fe (5)	−10–0	NMP	**2a** (50), **3a** (15)
7	*i*-Pr	FeCi$_3$ (5)	−10–0	NMP	**2a** (85)
8	*i*-Pr	Co (5)	−10–0	NMP	**2a** (42)

[a] 1.1 equivalents of RMgX

[b] Fe(acac)$_3$ or Co(acac)$_2$ (x% molar).

[c] THF with cosolvent.

[d] NR: no reaction.

desired *E*-bromoalkene product **2a** (49%), together with some coupled product 1-(2-quinolyl)-3-methyl-1-butene (5%). However, increasing the amount of catalyst to 20 mol% (result not shown) did not improve the yield of **2a** compared to the experiment with 5% of catalyst.

Another experiment (entry 6) showed that *n*-dodecylmagnesium bromide gives the same reaction, since the desired compound **2a** was isolated in 50% yield together with the cross-coupled product **3a** in 15% yield, resulting from the Grignard coupling reaction with the so-formed 1-bromo-1-alkene (**2a**), as reported by Cahiez [3a]. This result, with those obtained entry 5, shows that the reduction step is much more rapid than the coupling reaction with the so-formed 1-bromo-1-alkene (**2a**). When *n*-dodecylmagnesium bromide was used, we also isolated dodec-1-ene (3%).

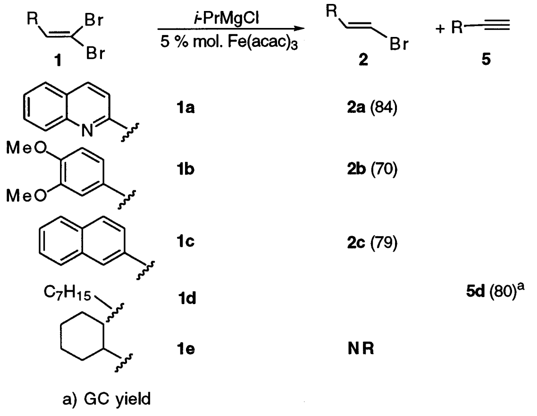
These results indicate that experiments probably proceeded through a hydrogen β elimination, leading to an hydridoiron (**I**) species which in turn is the reactive species. Felkin, when reducing allylic alcohols with Grignard reagents in the presence of a Ni(II) catalyst, proposed an hydridonickel intermediate [4]. Kochi assumed that Fe(III) was also reduced easily by Grignard reagents to afford an hydridoiron (**I**) complex [3b].

When FeCl$_3$ was used instead, **2a** was obtained in 85% yield, but FeCl$_3$ is not as convenient as Fe(acac)$_3$ because of its hydrophilic properties. We then tried Co(acac)$_2$ as catalyst for this reaction, since Co(II) is isoelectronic to Fe(I), and observed that in this case the desired 1-bromo-1-alkene (**2a**) was obtained in lower yield (42%), together with 1-(2-quinolyl)-3-methyl-1-butene (5%).

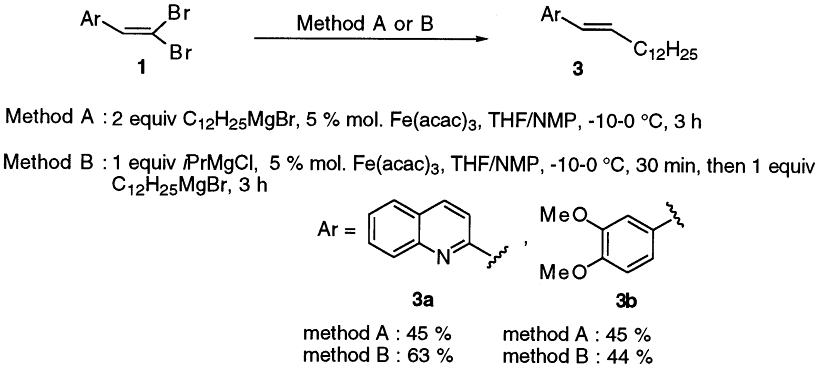
Then several 1,1-dibromo-1-alkenes (**1**) were treated under the best reaction conditions (Fe(acac)$_3$ 5% molar in a 1:1 THF + NMP mixture with one equivalent of *i*-PrMgCl for 30 min between − 10°C and 0°C) and the results are reported in Scheme 2.

It is worth noting that with aromatic alkenes, yields of the *E*-bromoalkenes **2a**–**c** obtained are good and the stereoselectivity excellent (no *Z*-isomers observed on the crude ^{1}H-NMR). However in the case of aliphatic 1,1-dibromo-1-alkenes (**1d**,**e**), either the corresponding alkyne was sometimes obtained, or no reaction occurred. In the case of 1,1-dibromo-1,3-dienes (results not shown) the expected reduced products are obtained but in lower yields, and thus further optimizations will be reported shortly.

The mechanism of this reaction is still unknown, but two observations should be made regarding the crucial effect of NMP which was also noted in related reactions [3a,5]. The influence of NMP in our reaction is highlighted by a comparison with the lack of reduction reaction in the iron-catalyzed olefin carbometalation with Grignard reagents in THF, as reported by Nakamura [6]. The second remark is the high *E* stereoselectivity observed, since all intermolecular oxidative additions of transition metal to 1,1-dihalo-1-alkenes have occurred onto the *trans* alkenyl-halide bond in all cases [7]. Only in intramolecular reactions the (*Z*)-bromide reacted with an organostannane [8]. A direct metalation via bromide–magnesium exchange is probably not involved at such a temperature [9], but a carbene species (through a Fritsch–Buttenberg–Wiechell rearrangement) could interfere in the cases of



Scheme 2.



Scheme 3.

non aromatic 1,1-dibromo-1-alkenes. Nevertheless further studies are required to elucidate this mechanism.

Then, we decided to study the possibility to perform the reduction and the cross-coupling reaction in a one-pot sequence by treating 1,1-dibromo-2-aryl-1-ethenes (**1**) either by two equivalents of a Grignard reagent in the presence of Fe(acac)$_3$ (5%), or by one equivalent of *i*-PrMgCl followed by one equivalent of the desired Grignard reagent (Scheme 3). The study was performed with 1,1-dibromo-2-quinolyl-1-ethene (**1a**) and with 1,1-dibromo-2-(3,4-dimethoxy)phenyl-1-ethene (**1b**) and $C_{12}H_{25}MgBr$. The expected *E*-1-aryl-tetradec-1-enes (**3a**,**b**) were thus obtained in moderate yields (not optimized).

When **1a** was treated directly by two equivalents of $C_{12}H_{25}MgBr$ (method A), compound **3a** was obtained in 45% yield, and dodec-1-ene was isolated in 9% yield. However, when **1a** was first treated by one equivalent of *i*-PrMgCl and then one equivalent of $C_{12}H_{25}MgBr$ (method B), **2a** was isolated in 63% yield. It is worth noting that **3b** was obtained in 45% yield whatever method (A or B) was used. We tentatively tried to increase the yield obtained through method B by using, in the second addition, either two equivalents of the Grignard reagent, or by adding 5% of fresh Fe(acac)$_3$, without success (result not shown). Finally when **1a** was treated through method B but using one equivalent of phenylmagnesium bromide instead of *n*-dodecylmagnesium bromide, 1-(2-quinolyl)-2-phenylethene (compound **3f** [10]) was obtained in 47% yield (not optimized).

In conclusion, we have shown that alkylmagnesium halides in the presence of iron(III) catalyst (or cobalt(II) catalyst) can reduce 1,1-dibromo-2-aryl-1-alkenes in good yields and excellent stereoselectivity, to afford the corresponding *E*-1-bromo-1-alkenes which can be further used in transition metal catalyzed cross-coupling reactions with organometallic species. However, this reaction seems limited, so far, to the conjugated alkenes. Further studies are in progress to define the scope and limitation of this new chemical transformation. Furthermore, this method is complementary to the palladium catalyzed *n*-Bu_3SnH-hydrogenolysis of these substrates [1c].

3. Experimental

All reactions were performed under nitrogen. THF was distilled in the presence of sodium and benzophenone. NMP was distilled prior to use. The 1,1-dibromoalkenes were synthesized from the corresponding aldehydes by treatment with carbon tetrabromide and triphenylphosphine in methylene chloride [11]. *i*-PrMgCl was purchased from Aldrich® and *n*-dodecylmagnesium bromide was prepared according to the usual procedure. Fe(acac)$_3$ and Co(acac)$_2$ (purchased from Aldrich®) were dried at 100°C for 3 h prior to use, whereas $FeCl_3$ was dried at 100°C under low pressure for several hours. ^1H- and ^{13}C-NMR spectra were registered at 200 and 50 MHz, respectively, on a Bruker AC-200 P spectrometer, and the ^1H–^1H (COSY-DQF, HOHAHA) and ^1H–^{13}C (HMQC and HMBC) correlation spectra at 400 MHz, on a Bruker ARX-400 spectrometer. Chemical shifts are reported as δ values (in parts per million), relative to the residual nondeuterated solvent signals as internal standard. The splitting pattern abbreviations are as follows: s = singlet, d = doublet, dd = double doublet, t = triplet, q = quadriplet, m = multiplet.

*3.1. Preparation of 1-bromo-1-alkenes (**2**) by reduction of l,1-dibromo-1-alkenes (**1**)*

*3.1.1. 1-Bromo-2-(2-quinolyl)ethene (**2a**)*

An orange–red solution of 1,1-dibromoalkene (**1a**) (0.200 g, 6.38×10^{-4} mol) with Fe(acac)$_3$ (11.28 mg, 3.19×10^{-5} mol, 5 mol%) in 3 ml of THF and 3 ml of NMP was cooled to −10°C and *iso*-propylmagnesium chloride (0.4 ml, 1.8 M, 1.1 equivalents, 7.2×10^{-4} mol) was added dropwise to immediately afford a dark brown solution. After 30 min of stirrring, 10 ml of water was introduced and the mixture warmed to room temperature (r.t.). The reaction mixture was extracted with ethyl ether (3 × 30 ml) and the organic layers were combined, washed with an aqueous saturated solution of $NaHCO_3$, then with brine and dried over $MgSO_4$. After filtration and evaporation of the solvents, the crude mixture was purified by flash chromatography (hexane/EtOAc 92:8) to afford 0.125 g (84%) of **2**a: ^1H-NMR (200 MHz, $CDCl_3$) δ: 7.36 (d, 1H, $J = 8.4$ Hz), 7.37 (d, 1H, $J = 15.9$ Hz), 7.50 (d, 1H, $J = 13.9$ Hz), 7.52 (t, 1H, $J = 3.6$ Hz), 7.70 (t, 1H, $J = 7.5$ Hz), 7.76 (d, 1H, $J = 8.1$ Hz), 8.04 (d, 1H, $J = 8.5$ Hz), 8.10 (d, 1H, $J = 8.4$ Hz); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 154.00, 147.06, 137.53, 136.71, 129.97, 129.35, 127.51, 126.75, 126.51, 119.24, 114.14; MS-ESI m/z: 235 ([M^+], 100), 234 (78).

3.1.2. 1-Bromo-2-(3,4-dimethoxyphenyl)ethene (**2b**)

Prepared and purified in the same manner as described for **2a** from **1b** (0.200 g, 6.21×10^{-4} mol) with $Fe(acac)_3$ (10 mg, 3.10×10^{-5} mol, 5 mol%). The crude mixture was purified by flash chromatography (hexane/EtOAc 85:15) to afford 0.122 g (70%) of **2b**: ^1H-NMR (200 MHz, $CDCl_3$) δ: 7.02 (d, 1H, $J = 14.1$ Hz), 6.80 (m, 3H), 6.61 (d, 1H, $1 = 13.7$ Hz), 3.87 (s, 6H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 149.28, 149.07, 136.70, 128.94, 119.29, 111.15, 108.58, 55.78; MS-EI m/z: 244 ([M^+], 92), 242 (100), 229 (38), 227 (40), 120 (82).

3.1.3. 1-Bromo-2-(2-naphthyl)ethene (**2c**)

Prepared and purified in the same manner as described for **2a** from **1c** (0.150 g, 4.82×10^{-4} mol) with $Fe(acac)_3$ (8.5 mg, 2.41×10^{-5} mol, 5 mol%). The crude mixture was purified by flash chromatography (hexane) to afford 0.087 g (79%) of **2c**: ^1H-NMR (200 MHz, $CDCl_3$) δ: 7.82 (m, 4H), 7.49 (m, 3H), 7.27 (d, 1H, $J = 14.0$ Hz), 6.90 (d, 1H, $J = 14.0$ Hz); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 154.0, 147.06, 137.33, 128.59, 128.34, 128.13, 127.78, 126.63, 126.38, 122.96, 106.88; MS-EI m/z: 234 ([M^+], 71), 232 (77), 198 (55), 172 (77), 155 (61), 127 (100).

3.2. Preparation of alkenes **3** by reduction and cross-coupling reactions of 1,1-dibromo-1-alkenes (**1**) with $C_{12}H_{25}MgBr$

3.2.1. 1-(2-Quinolyl)tetradecene (**3a**)

Method A: an orange–red solution of 1,1-dibromoalkene (**1a**) (0.100 g, 3.19×10^{-4} mol) with $Fe(acac)_3$ (5.6 mg, 1.59×10^{-5} mol, 5 mol%) in 2 ml of THF and 2 ml of NMP was cooled to −10°C and $C_{12}H_{25}MgBr$ (6.4 ml, 0.1 M, 2.1 equivalents, 6.4×10^{-4} mol) was added dropwise, to immediately afford a dark brown solution. After 3 h of stirring, 5 ml of water was introduced and the mixture warmed to r.t. The reaction mixture was extracted with ethyl ether (3 × 10 ml) and the organic layers were combined, washed with an aqueous saturated solution of $NaHCO_3$, then with brine and dried over $MgSO_4$. Alter filtration and evaporation of the solvents, the crude mixture was purified by flash chromatography (hexane/EtOAc 95:5) to afford 0.047 g (45%) of **3a**.

Method B: an orange–red solution of 1,1-dibromoalkene (**1a**) (0.200 g, 6.38×10^{-4} mol) with $Fe(acac)_3$ (16.4 mg, 4.65×10^{-5} mol, 5 mol%) in 3 ml of THF and 3 ml of NMP was cooled to −10°C and *iso*-propylmagnesium chloride (0.47 ml, 1.5 M, 1.1 equivalents, 7.1×10^{-4} mol) was added dropwise to immediately afford a dark brown solution. After 30 min of stirring $C_{12}H_{25}MgBr$ (2.8 ml, 0.25 M, 1.1 equivalents, 7.02×10^{-4} mol) was added dropwise. After 3 h of stirring, 5 ml of water were introduced and the mixture warmed to r.t. The reaction mixture was extracted with ethyl ether (3 × 10 ml) and the organic layers were combined, washed with an aqueous saturated solution of $NaHCO_3$, then with brine and dried over $MgSO_4$. After filtration and evaporation of the solvents, the crude mixture was purified by flash chromatography (hexane/EtOAc 95:5) to afford 0.129 g (63%) of **3a**.

^1H-NMR (200 MHz, $CDCl_3$) δ: 8.06 (d, 1H, $J = 8.2$ Hz), 8.02 (d, 2H, $J = 6.9$ Hz), 7.75 (d, 1H, $J = 8.4$ Hz), 7.67 (ddd, 1H, $J = 8.4$, 7.2, 1.2 Hz), 7.52 (d, 1H, $J = 8.9$ Hz), 7.46 (dd, 1H, $J = 8.9$, 7.1 Hz), 6.84 (dt, 1H, $J = 15.8$, 6.0 Hz), 6.70 (d, 1H, $J = 16.1$ Hz), 2.32 (q, 2H, $J = 7.2$ Hz), 1.56 (m, 2H), 1.26 (m, 18H), 0.87 (t, 3H, $J = 6.6$ Hz); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 156.40, 148.01, 137.90, 135.97, 130.96, 129.36, 129.04, 127.29, 127.05, 125.67, 118.58, 33.00, 30.87, 29.62, 29.30, 28.86, 22.63, 14.04; MS-ESI m/z: 324 ([MH^+]).

3.2.2. 1-(3,4-Dimethoxyphenyl)tetradecene (**3b**)

Method A: prepared and purified in the same manner as described for **3a** from **1b** (0.300 g, 9.31×10^{-4} mol). The crude mixture was purified by flash chromatography (hexane/EtOAc 92:8) to afford 0.139 g (45%) of **3b**. Method B: an orange–red solution of 1,1-dibromoalkene (**1b**) (0.300 g, 9.31×10^{-4} mol) with $Fe(acac)_3$ (16.4 mg, 4.65×10^{-5} mol, 5 mol%) in 4 ml of THF and 4 ml of NMP was cooled to −10°C and *iso*-propylmagnesium chloride (0.5 ml, 2 M, 1.1 equivalents, 1.0×10^{-4} mol) was added dropwise to immediately afford a dark brown solution. After 30 min of stirring, $C_{12}H_{25}MgBr$ (4 ml, 0.25 M, 1.0×10^{-3} mol, 1.1 equivalents) was added dropwise. After 3 h, 10 ml of water were introduced and the mixture warmed to r.t. The reaction mixture was extracted with ethyl ether (3 × 30 ml) and the organic layers were combined, washed with an aqueous saturated solution of $NaHCO_3$, then with brine and dried over $MgSO_4$. After filtration and evaporation of the solvents, the crude mixture was purified by flash chromatography (hexane/EtOAc 92:8) to afford 0.138 g (44%) of **3b**.

^{1}H-NMR (200 MHz, CDCl$_3$) δ: 6.90–6.75 (m, 3H), 6.31 (d, 1H, $J = 16.2$ Hz), 6.12 (dt, 1H, $J = 16.2$, 6.6 Hz), 3.89 (s, 3H), 3.85 (s, 3H), 2.18 (q, 2H, $J = 6.8$ Hz), 1.26 (m, 20H), 0.88 (t, 3H, $J = 6.2$ Hz); ^{13}C-NMR (50 MHz, CDCl$_3$) δ: 148.95, 148.15, 131.12, 129.26, 118.71, 111.16, 108.52, 55.83, 55.71, 32.95, 31.88, 29.51, 29.31, 29.28, 22.61, 14.03; MS-EI m/z: 332 ([M$^+$], 26), 177 (100).

Acknowledgements

J.C. Jullian is acknowledged for the NMR analyses, Dr O. Laprévote and L. Serani for the MS experiments. Thanks are due to Dr M. Alami for fruitful discussions.

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