Regio- and Stereoselective Preparation of β,γ-Unsaturated Carboxylic Acids by One-Pot Sequential Double 1,6-Addition of Grignard Reagents to Methyl Coumalate

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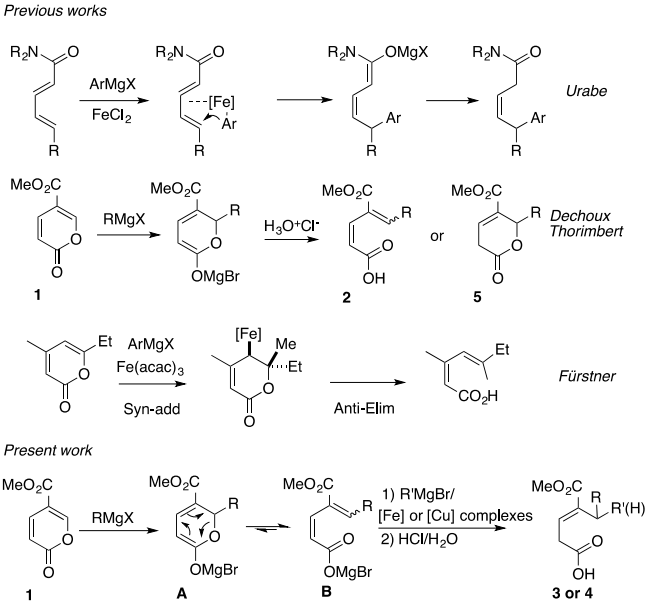
Abstract: An efficient regio- and stereo-selective metal-catalyzed addition of two Grignard reagents (homo-coupling, 2 RMgX or hetero-coupling, $R^1MgX + R^2MgX$) to methyl coumalate is described. This synthetic approach opens access to a wide variety of functionalized β,γ-unsaturated carboxylic acids in a modular way. Control of the chemo- and stereoselectivity of this one-pot procedure is discussed.

Introduction

While numerous conjugate additions of Grignard reagents to *α,β*-unsaturated carbonyl compounds have been described,[1] far less reports were devoted to the conjugate addition to *α,β,γ,δ*-di-unsaturated systems.[2,3] The reasons of this poor investigation are presumably due to the numerous issues to control i) the regioselectivity of addition (1,4- *versus* 1,6-) ii) the regioselectivity of reprotonation (giving access to *α,β*- or *β,γ*-unsaturated carbonyl derivatives) and iii) the configuration of the newly formed double bond. Only an handful number of copper-catalyzed 1,6-additions on dienoates[4] and dienones[5] have been reported. For instance, the group of Urabe reported rare examples of 1,6-conjugate additions on unsaturated amides using an iron catalyst ($FeCl_2$).[6] They observed regio- and stereo-selective formation of *β,γ*-unsaturated carbonyl products. They proposed a mechanism involving η^4-complexation of the iron complex that could explain the total stereoselectivity observed for the reaction (Scheme 1).

□□□□□-pyrone derivatives[7] such as methyl coumalate **1** can be considered as cyclic dienoate compounds.[8] We recently reported the efficient and stereoselective synthesis of conjugated (*Z*,*Z*) or (*Z*,*E*)-dienoic acids **2** by regioselective 1,6-addition of Grignard reagents (1 equiv.) to methyl coumalate **1** (Scheme 1).[9].

Concomitantly to our study, Fürstner[7b] published the regio- and stereoselective 1,6-addition of Grignard reagents in excess to substituted 2-pyrones in the presence of a catalytic amount of $[Fe(acac)_3]$. The reaction mechanism suggested by Fürstner involved the stepwise formation of a η^4-dienic iron complex followed by *syn*-selective 1,2-insertion of the π-system into the Fe-Me bond and further *anti*-elimination (Scheme 1).



Scheme 1. Stereoselective synthesis of unsaturated acids.

Here we report a novel one-pot, three-step, double 1,6 conjugate addition[10] to methyl coumalate affording a wide variety of functionalized *β,γ*-unsaturated carboxylic acids **3** or **4** in a modular way (Scheme 1).[11] The pivotal role of the catalyst ($[Fe(acac)_3]$ or $Cu(OTf)_2$) in the regio- and stereo-chemical control of the reaction, owing to the activation of putative intermediate **B,** will be presented.

Results and Discussion

First, we investigated the conjugate addition of an excess of various Grignard reagents in the presence of TMSCl in THF at 0 °C (Table 1, entries 3,6,13). Interestingly, under these conditions, methyl Grignard reagent did not give the expected product **3** (see SI for attribution) and when sterically hindered nucleophiles such as *i*-PrMgBr or *t*-BuMgCl were used, the reaction stopped after the first addition. In these cases the *α-Z*/*γ-E*-dienoic acids **2d-e** were obtained as well as their

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corresponding lactones **5** (see SI for full details).[9] These first results indicate that in the absence of catalyst, bulky Grignard reagents do not add to the putative 2,4-dienic magnesium carboxylate **B** (Scheme 1). On the other hand, double addition of EtMgBr, *n*-BuMgBr and PhMgBr at the 6-position of methyl coumalate occurred, giving the expected β,γ-unsaturated carboxylic acids **3b,c,f** in 30, 92 and 90 % yield respectively, with *E*/*Z* ratios close to 80/20. Assignment of the configuration of the β,γ-double bond in (*Z*)-**3b,c** and (*E*)- **3b,c** was achieved by NOESY experiments (strong correlation between H^a and H^d in the *E* isomers). It is noteworthy that in all ^{1}H NMR spectra, proton H^b of (*E*)-**3** was deshielded at around 7 ppm versus 6 ppm for (Z)-**3** (Figure 1, for full details see SI).

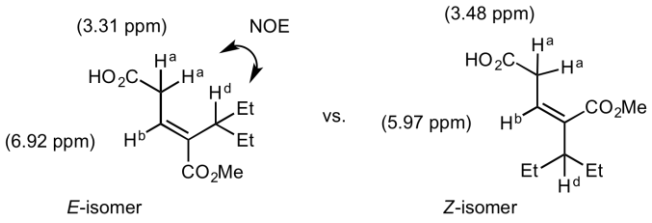


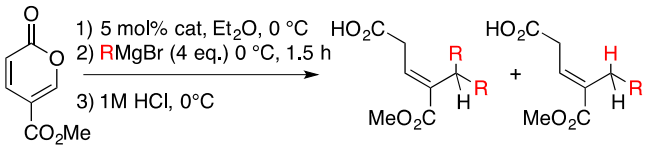
Figure 1. Example of assignment of configuration for compound **3b**.

We surmised that the presence of Lewis acidic salts could favor the 6-π electrocyclic opening of intermediate **A** into **B** as well as activate both the nucleophiles and the electrophiles. We thus turned our attention to the possible iron- or copper-catalyzed double addition (Table 1).[12] In a typical experiment, methyl coumalate **1** was treated with 4 equiv. of MeMgBr in Et_2O at 0 °C in the presence of 5 mol % catalyst ($Cu(OTf)_2$ or $[Fe(acac)_3]$). After 1.5 hour and acidic quench, the β,γ-unsaturated acid (*E*)-**3a** was obtained in good yield and excellent regio- and stereoselectivity (Table 1, entries 1-2).

Data gathered in Table 1 highlight the scope and limitations of this homo-double addition. Under these new conditions, using either copper or iron catalysis, the expected double 1,6-addition was more general and gave better stereoselectivity. In the case of primary (Me, Et, *n*-Bu) or phenyl Grignard reagents and $Cu(OTf)_2$ as catalyst, the expected β,γ-unsaturated carboxylic acids **3a-c,f** were now isolated in high yields and excellent stereoselectivity (Table 1, entries 2,5,8). The iron catalyst was slightly less efficient than the copper one, since it resulted the formation of by-products or in one case formation of products **4c** arising from 1,6-addition of hydride (Table 1, entries 4,7,9). Secondary and tertiary Grignard reagents afforded the α,β-unsaturated acids **4d-e** using both catalysts (Table 1, entries 10,12).[13]

The presence of the ester moiety on the carbon-5 of methyl coumalate seems to be essential for the double addition on carbon-6 to occur. Indeed, α-pyrone reacted with PhMgBr in the presence of $[Fe(acac)_3]$ or $Cu(OTf)_2$ to give mixture of 1,4 and 1,6-addition products in low yields. Starting from methyl-2-pyron-3-carboxylate, PhMgBr provided the 1,4-addition product whatever the catalyst used (**8f**-**10f**, for full details see SI).

Table 1. One-pot metal-catalyzed double 1,6-addition of Grignard reagents



1 **3** **4**

Entry	R	Catalyst	Products (yield %)	*E*/*Z* ratio[c]
1	Me	$Fe(acac)_3$	**3a** (76)	>95/5
2	Me	$Cu(OTf)_2$	**3a** (90)	>95/5
3	Et	/[a]	**3b** (30)	82/18
4	Et	$Fe(acac)_3$	**3b** (56)	>95/5
5	Et	$Cu(OTf)_2$	**3b** (92)	>95/5
6	*n*-Bu	/[a]	**3c** (92)	80/20
7	*n*-Bu	$Fe(acac)_3$	**3c**/**4c** (70) [b]	>95/5
8	*n*-Bu	$Cu(OTf)_2$	**3c** (98)	>95/5
9	*i*-Pr	$Fe(acac)_3$	/	/
10	*i*-Pr	$Cu(OTf)_2$	**3d**/**4d** (60/40) [b]	/
11	*t*-Bu	$Fe(acac)_3$	**4e** (66)	>95/5
12	*t*-Bu	$Cu(OTf)_2$	**4e** (72)	>95/5
13	Ph	/[a]	**3f** (90)	79/21
14	Ph	$Fe(acac)_3$	**3f** (90)	>95/5
15	Ph	$Cu(OTf)_2$	**3f** (95)	>95/5

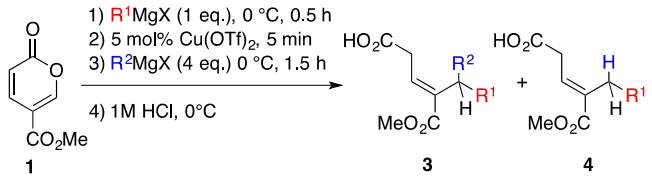
[a] No catalyst but 1 equiv.of Me_3SiCl. [b] Total conversion, estimated yield based on ^{1}H NMR of the crude. [c] Determined by ^{1}H NMR of the crude.

Next we examined the outcome of the copper catalyzed one-pot reaction by using successively two different Grignard reagents (Table 2). We focused our attention on the use of $Cu(OTf)_2$, as we initially observed lower yields with $[Fe(acac)_3]$ (*vide supra*, Table 1). Due to obvious chemoselectivity issues, one equivalent of the first Grignard reagent was added before addition of catalyst (in order to ensure efficient formation of the mono-adduct (carboxylate **B**) and to avoid formation of the homo-coupling adduct. The new conditions were as follows: 1.1 equivalent of the first Grignard reagent was added without catalyst, then 5 mol % of $Cu(OTf)_2$, followed by addition of 4 equiv. of the second Grignard reagent.

Data in Table 2 illustrate the scope and limitations of the hetero-coupling method. In almost all cases, good yields and good to excellent stereoselectivities were attained. When MeMgBr or PhMgBr were added first, the expected β,γ-unsaturated acids **3i-q** were obtained as the *E*-isomers with good diastereoselectivity (Table 2, entries 1-9). With primary, secondary and tertiary

Grignard reagents as first nucleophile, the outcome of the reaction depended on the structure of the second nucleophile (Table 2, entries 10-21). When MeMgBr was used as second nucleophile, the reaction gave the expected product **3** in low yield (Table 2, entries 5,10,15, see also SI, table S1 for more data). In contrast, the addition of phenyl and vinyl Grignard as second nucleophiles was successfully achieved affording compounds **3i,m,n,o,p,q,s,u,w** in moderate to good yield (Table 2, entry 1,4,9,13,14,18,19,22,23).

Table 2. Selective one-pot copper-catalyzed hetero double 1,6-addition.

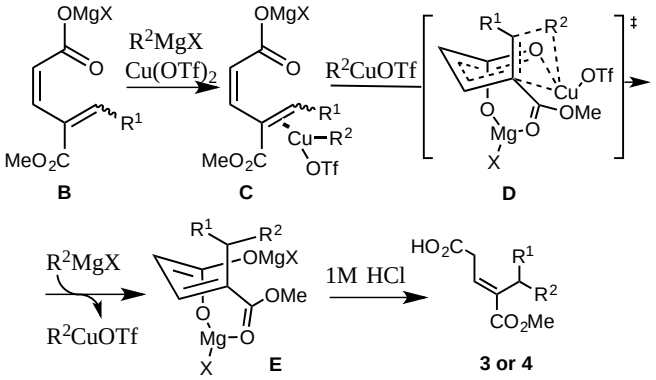


Entry	R^1	R^2	Products (yield %)	*E*/*Z* ratio[b]
1	Me	Ph	**3i** (71)	93/7
2	Me	*n*-Bu	**3k** (74)	94/6
3	Me	*i*-Pr	**3l** (90)	86/14
4	Me	vinyl	**3m** (61)	79/21
5	Ph	Me	degrad.	/
6	Ph	*n*-Bu	**3n** (68)	93/7
7	Ph	*i*-Pr	**3o** (59)	>95/5
8	Ph	*t*-Bu	**3p** (76)	>95/5
9	Ph	vinyl	**3q** (67)	80/20
10	*n*-Bu	Me	**3k** (30) [a]	/
11	*n*-Bu	*i*-Pr	**3r** (89)	91/9
12	*n*-Bu	*t*-Bu	/	/
13	*n*-Bu	Ph	**3n** (25) [a]	/
14	*n*-Bu	vinyl	**3s** (29)	89/11
15	*i*-Pr	Me	degrad.	/
16	*i*-Pr	*n*-Bu	**3r** (98)	>95/5
17	*i*-Pr	*t*-Bu	**3t/4d** (52/48) [b]	/
18	*i*-Pr	Ph	**3o** (31)	>95/5
19	*i*-Pr	vinyl	**3u** (52)	>95/5
20	*t*-Bu	*n*-Bu	**4e** (19) [a]	>95/5
21	*t*-Bu	*i*-Pr	**4e** (82)	>95/5
22	*t*-Bu	Ph	**3p** (76)	>95/5
23	*t*-Bu	vinyl	**3w** (39)	>95/5

[a] Total conversion, estimated yield based on ^{1}H NMR of the crude product. [b] Determined by ^{1}H NMR of the crude product.

Concerning the chemoselective C- *versus* H- addition during the second step, Me-, Ph- and vinyl-Grignard reagents afforded the expected double alkylated products **3** (obviously, there is no possible β-hydride elimination). In the case of Grignard reagents bearing a β-hydride, the course of the reaction changed and depended on the bulkiness of the first introduced alkyl group. Indeed, inversion of the order of addition of *i*-PrMgBr and *t*-BuMgCl led to inversion of the chemoselectivity (Table 2, entries 17, 21). More generally, introduction of a first bulky alkyl group favored the hydride addition except when β-hydride elimination of the second Grignard reagent was impossible (Table 2, entries 21 vs. 22).

Concerning the mechanism of this multi-step reaction, the steroselectivity of the process should give us some clues.[14] Notably, we should take into account the difference of stereo outcome observed between the reactions with or without metal catalysis (Table 1, for more details see SI, spectra of compound **3b** page S9). Furthermore, occurrence of a thermodynamic equilibrium between the stereoisomers during acid treatment of the reactions was ruled out. Indeed, even the reaction mixture was hydrolyzed overnight (entry 6 in Table 2) with 1M HCl or when the reaction was quenched with higher concentrations of aqueous HCl, no change of the stereoisomeric ratio was observed (*E*/*Z* = 97/3). We propose the involvement of a highly chelated transition state **D** in the second step of the reaction (Scheme 2).



Scheme 2. Proposed mechanism for copper-catalyzed stereoselective addition leading to acids **3** and **7**.

As previously demonstrated,[9] addition of the first Grignard reagent gives intermediate **B** resulting in complex **C** by reaction with the organocopper complex (R^2CuOTf). Addition of the second Grignard reagent leads to a chair-like bicyclic transition

state **D** locking the overall stereoselectivity. Axial positioning of the alkyl chain and equatorial positioning of the methyl ester group could be rationalized by the presence of a stabilizing electronic interaction through the formation of a 8-membered pseudo-cycle. Further transmetalation may give access to a stabilized bimetallic cyclic intermediate **E**. In this stabilized intermediate, the non-planarity of the two C-C double bonds explains both the kinetic control (no change in the stereoselectivity with time) and the total regiocontrol of the reprotonation (α *versus* γ) giving the β,γ unsaturated acids **3** or **7** as unique regioisomers.

Conclusions

In summary, we have developed a one-pot sequential double alkyl-alkyl or alkyl-hydride 1,6-addition starting from methyl coumalate. This is a valuable method for the preparation of β,γ-unsaturated carboxylic acids in a highly regio-, chemo- and stereoselective manner.[11] We also elucidated the pivotal role of the Grignard reagent as regards the stereoselectivity outcome of the reaction. The later could be rationalized by invoking a constrained chair-like transition state with the formation of a stable bimetallic intermediate.

Experimental Section

General method for homocoupling.

To a solution of methyl coumalate (308 mg, 2 mmol) in dry Et_2O (25 mL) at 0 °C, under argon atmosphere, $Cu(OTf)_2$ (36 mg, 0.1 mmol) or $Fe(acac)_3$ (35 mg, 0.1 mmol) was added, followed by R^1MgX (8 mmol) by dropwise addition (5 – 10 min). The mixture was stirred for 1.5 h, then quenched at 0 °C with saturated aq. NH_4Cl solution and washed with dichloromethane (2 × 20 mL). The aqueous layer, was then acidified with 1M HCl (until pH = 1 – 2) and extracted with CH_2Cl_2 (3 × 20 mL). Combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to afford target product.

(E/Z)-4-(methoxycarbonyl)-5-methylhex-3-enoic acid (**3a**)

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 6.70 (t, *J* = 7.2 Hz, 1H, H_b); 3.71 (s, 3H, OMe); 3.31 (d, *J* = 7.2 Hz, 2H, 2×H_a); 2.86 – 2.79 (m, 1H, H_d); 1.20 (s, 3H, CH_3); 1.18 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 176.1; 167.5; 141.1; 130.3; 51.6; 33.1; 28.1; 20.7. HRMS (ESI-MS) calcd for $C_9H_{14}O_4Na$ $[M+Na]^+$ = 209.0790, Found 209.0796.

General method for heterocoupling.

To a solution of methyl coumalate (308 mg, 2 mmol) in dry Et_2O (25 mL) at 0 °C, under argon atmosphere, R^1MgX (2.2 mmol) was added dropwise (5 – 10 min) and the mixture stirred for 0.5 h. Then $Cu(OTf)_2$ (36 mg, 0.1 mmol) was added and mixture was further stirred for 5 min. R^2MgX (8 mmol) was added dropwise (5 min) and the solution stirred for 1.5 h at 0 °C. The reaction mixture was quenched at 0 °C with 1M HCl (until pH = 1 – 2) diluted with ethyl acetate (20 mL) and separated. The organic layer was washed once with 1M HCl (6 mL) and filtered through celite. Combined organic layers were evaporated under reduced pressure to afford target acid.

(E/Z)-4-(methoxycarbonyl)-5-phenylhex-3-enoic acid (**3i**)

Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): *E*-isomer: δ 7.25 (s, 5H, Ph); 6.92 (t, *J* = 7.2 Hz, 1H, H_b); 4.17 (q, *J* = 7.2 Hz, 1H, H_d); 3.67 (s, 3H, OMe); 3.26 (dd, *J* = 18.5 Hz, *J* = 7.2 Hz, 1H, H_a); 3.16 (dd, *J* = 18.4 Hz, *J* = 7.1 Hz, 1H, $H_{a'}$); 1.57 (d, *J* = 7.2 Hz, 3H, CH_3); *Z*-isomer (significant signals): δ 6.14 (t, *J* = 7.9 Hz, 1H, H_b). ^{13}C NMR (100 MHz, $CDCl_3$): *E*-isomer: δ 175.7; 167.3; 143.1; 139.7; 132.5; 128.4; 127.3; 126.2; 51.9; 37.0, 33.4; 31.0; 17.8. HRMS (ESI-MS) calcd for $C_{14}H_{16}O_4Li$ $[M+Li]^+$ = 255.1203, Found 255.1213.

Acknowledgements

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Keywords: unsaturated acids • 6-π electrocyclic ring opening • double 1,6-conjugate addition • metal catalysis • Grignard reagent

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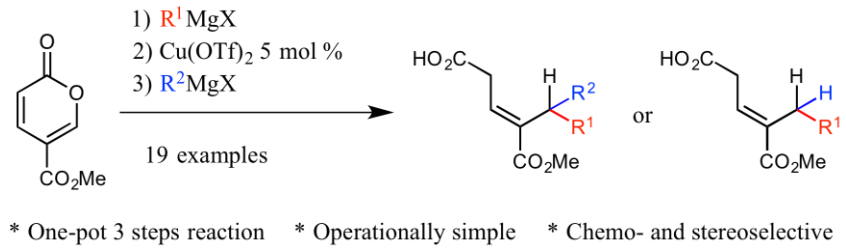

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Regio- and Stereoselective Preparation of *β,γ*-Unsaturated Carboxylic Acids by One-pot Sequential Double 1,6-Addition of Grignard Reagents to Methyl coumalate.

An efficient one-pot three-step reaction allowed the preparation of *β,γ*-unsaturated carboxylic acids with controlled stereochemistry.