JOC Article

Iron-Catalyzed Electrochemical Allylation of Carbonyl Compounds by Allylic Acetates

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Homoallylic alcohols were synthesized from aldehydes or ketones and allylic acetates, using an electrochemical process catalyzed by iron complexes. We first studied the reactivity of allyl acetate, using *N*,*N*-dimethylformamide (DMF) or acetonitrile (AN) as solvent, $FeBr_2$ as catalyst, and Fe as the sacrificial anode. Then we tested the regioreactivity of crotyl acetate and other allylic derivatives.

Introduction

Synthesis of homoallylic alcohols by allylation of carbonyl compounds is one of the most important processes in organic synthesis[1] since the homoallylic alcohols can be easily converted to many important building blocks for natural product synthesis.[2] Different methods have been developed based essentially on the nucleophilic character of the allylmetal obtained from allyl bromides and metallic species[3−7] (metal = Li, Mg, Al, Zn, Ni, ...). More recently, other allylic organometallic compounds have been examined, such as allylchromium,[8] -indium,[9] -manganese,[10] -silane,[11] -boronate,[12] -stannane,[13] etc. The allylation reaction with these new allylic organometallic compounds has been studied mostly with aldehydes but rarely with ketones because of the difference of reactivity between these two carbonyl groups. Whereas allylation reactions from allyl halides seem to proceed without major difficulties, the use of allylic acetate necessitates palladium as catalyst, in the presence of another metal or reducing salt.[14] Another access to allylic anions is their electrochemical generation. An electrochemical activation of allyl bromide with use of catalytic amounts of tin has also been reported[15] to yield homoallylic alcohols. In our laboratory, we have already describe some electrochemical processes for the synthesis of homoallylic alcohols.[16] We recently described[17] an electrosynthetic process for the Reformatsky reaction, catalyzed by iron complexes and using a sacrificial iron anode, that afford β-hydroxyesters with good to high yields from α-haloester and a variety of carbonyl compounds. We intend to show that this electrochemical method can be suitable for the activation of allyl acetates. We present in this paper the investigation of the iron-catalyzed electroreductive coupling reaction from allyl acetates with carbonyl compounds (Scheme 1), leading to homoallylic alcohols. The chemistry of allylic compounds also includes the additional regiochemical aspect.

Results and Discussion

We thus first conducted a series of experiments with allyl acetate and various carbonyl compounds (**1**−**9**) in the reaction conditions previously used for the Reformatsky reaction[17] (DMF at room temperature, with a current intensity of 250 mA, and having an iron rod as the sacrificial anode). Results are given in Table 1. Chemical yields are moderate to good. Therefore, the use of iron salts obtained during a preelectrolysis allows the cross-coupling between allyl acetate and carbonyl com-

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SCHEME 1. Addition of Allyl Acetate to Carbonyl Compounds via an Iron Catalysis

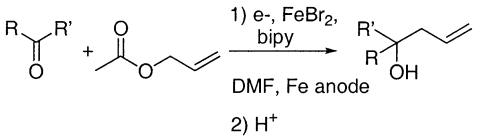


CHART 1. Carbonyl Compounds

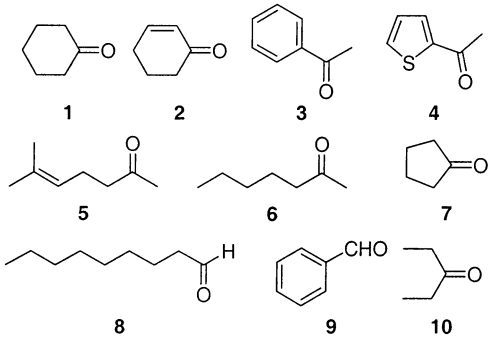
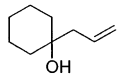
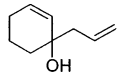
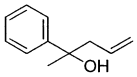
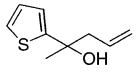
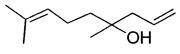
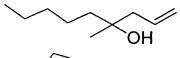
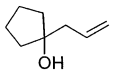
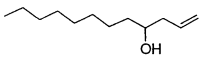
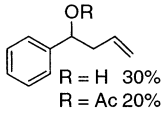


TABLE 1. Iron-Catalyzed Electroreductive Coupling between Allyl Acetate and Carbonyl Compounds[a]

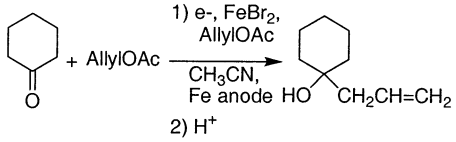
entry	Carbonyl compound	n_{eq} allylOAc	Isolated Yields (%) of coupling product[b]	
1	**1**	2		78
2	**2**	1.6		39[c]
3	**3**	1.9		86
4	**4**	2.2		65
5	**5**	2.8		66
6	**6**	2.4		60
7	**7**	3		63
8	**8**	2[d]		41
9	**9**	2[d]	 R = H 30% R = Ac 20%	50

[a] Typical procedure: carbonyl compounds (10 mmol), allyl acetate added constantly to the solution at 4.7 mmol/h, $FeBr_2$ obtained electrochemically by reduction of CH_2Br-CH_2Br (1 mmol), 2,2′-bipyridine (5 mmol), DMF (40 mL) + NBu_4BF_4 (0.6 mmol), room temperature, constant current intensity (250 mA), $Q = 4$ F/mol of carbonyl compounds, under argon, iron anode, and nickel-sponge cathode. [b] Isolated yields, based on initial carbonyl compounds. All products gave satisfactory analytical data. [c] No 1,4-addition product was detected. [d] 20 mmol of allyl acetate initially introduced, and RCHO was added via the syringe pump to minimize the direct reduction.

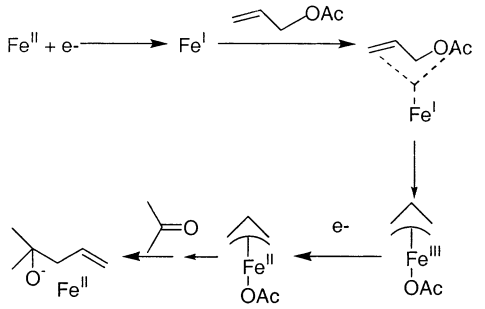
pounds. This method is efficient with aliphatic and cyclic, as well as aromatic ketones (Table 1, entries 1−7).

In the case of aldehydes (Table 1, entries 8 and 9), chemical yields are moderate due to pinacolization, and addition of the aldehyde via a syringe pump to the reaction mixture is necessary. With benzaldehyde **9**

SCHEME 2. Addition of Allyl Acetate to Cyclohexanone via Iron Catalysis, Using Allyl Acetate as Ligand



SCHEME 3. Proposed Mechanism of the Iron-Catalyzed Electrochemical Addition of Allyl Acetate to Carbonyl Compounds, Using Allyl Acetate as Ligand



(Table 1, entry 9), homoallylic alcohol is obtained together with its acetate. In all cases, a portion of the allyl acetate is recovered after the electrochemical reaction. Particularly, in the case of aldehydes, 20 mmol of allyl acetate is initially introduced, and 7 mmol was recovered.

Lower yields were obtained with 2-cyclohexen-1-one **2** even if the ketone is totally consumed (Table 1, entry 2), and no other products were detected. No conjugated addition was observed, thus indicating that the reaction is regiospecific.

We previously have shown that allyl acetate also could be used as a ligand instead of 2,2′-bipyridine.[17] Because of the environmental interest in avoiding 2,2′-bipyridine, we have tried to realize the cross-coupling reaction between cyclohexanone **1** and allyl acetate, using this compound as the reagent as well as the ligand of iron salts (Scheme 2). In this case, DMF could be replaced by acetonitrile.

We obtained, with 3 equiv of allyl acetate, an isolated yield of 73% of coupling product, instead of 78% with 2,2′-bipyridine (Table 1, entry 1), with the consumption of only 1 equiv of allyl acetate. So, chemical yields are similar with either 2,2′-bipyridine or allyl acetate as the ligand. Therefore, the substitution of 2,2′-bipyridine by allyl acetate does not significantly affect the chemical yield of the cross-coupling reaction. It is therefore obvious that, in this coupling reaction, the allyl acetate itself coordinates to iron salts, thus leading to an Fe^{I}- - - allylOAc intermediate, which is probably transformed into a π-allyl−iron complex before reacting with carbonyl compounds (Scheme 3).

Further investigations are necessary to determine which kind of organoiron species are involved. Moreover, we have run the reaction without carbonyl compounds. We only obtained, in this case, the formation of hexadiene, thus confirming the formation of the π-allyl−iron complex.

Then we wanted to test the regioreactivity of this coupling reaction. So we have run a series of experiments

SCHEME 4. Regioselectivity of the Iron-Catalyzed Electrochemical Addition of Crotyl Acetate to Carbonyl Compounds

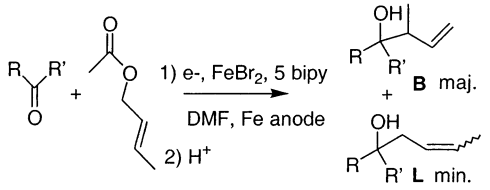


TABLE 2. Iron-Catalyzed Electroreductive Coupling between Allylic Compounds and Carbonyl Compounds[a]

entry	carbonyl compd	allylic compd (n_{eq})	yield (%) of coupling product[b]	ratio **B/L**
1	**1**	$CH_3CH{=}CHCH_2OAc$ (1.3)	92	98/2
2	**1**	$CH_2{=}CHCH(CH_3)OAc$ (1.2)	91	98/2
3	**7**	$CH_3CH{=}CHCH_2OAc$ (1.8)	60	97/3
4	**7**	$CH_2{=}CHCH(CH_3)OAc$ (1.4)	56	96/4
5	**7**	$CH_3CH{=}CHCH_2Cl$ (3.2)	35[c]	97/3
6	**3**	$CH_3CH{=}CHCH_2OAc$ (1)	93[d]	99/1
7	**3**	$CH_2{=}CHCH(CH_3)OAc$ (1)	88[d]	99/1
8	**3**	$CH_3CH{=}CHCH_2Cl$ (3.2)	64[d]	99/1
9	**10**	$CH_3CH{=}CHCH_2OAc$ (2.4)	87	98/2
10	**4**	$CH_3CH{=}CHCH_2OAc$ (2)	87[e]	99/1
11	**9**	$CH_2{=}CHCH(CH_3)OAc$ (2)[g]	58[f]	100/0
12	**8**	$CH_2{=}CHCH(CH_3)OAc$ (2)[g]	63[d]	100/0
13	**1**	$PhCH{=}CHCH_2OAc$ (1)	57	100/0
14	**10**	$(CH_3)_2C{=}CHCH_2OAc$ (1)	16	100/0
15	**1**	$(CH_3)_2C{=}CHCH_2OAc$ (0.64)	46	100/0

[a] Typical procedure: carbonyl compounds (10 mmol), allylic compounds added constantly to the solution at 4.0 mmol/h, $FeBr_2$ obtained electrochemically by reduction of $CH_2Br{-}CH_2Br$ (1 mmol), 2,2′-bipyridine (5 mmol), DMF (40 mL) + NBu_4BF_4 (0.6 mmol), room temperature, constant current intensity (250 mA), $Q = 4$ F/mol of carbonyl compounds, under argon, iron anode, and nickel-sponge cathode. [b] Isolated yields, based on initial carbonyl compounds. All products gave satisfactory analytical data. [c] 58% of unreacted ketone is recovered. [d] Product **B**: erythro/threo 57/43. [e] Product **B**: erythro/threo 50/50. [f] Product **B**: erythro/threo 63/37. [g] 20 mmol of allylic acetate initially introduced, and RCHO was added via the syringe pump to minimize the direct reduction.

with the same experimental procedure, using crotyl acetate (or its allylic isomer) instead of allyl acetate. Reactions involving allylic derivatives generally give two isomeric products due to allylic transposition (Scheme 4).

The ratio of branched to linear alcohol (**B**/**L**) is known to depend mainly on the nature of the metal in the organometallic reagent.[1,18] However, in this method, the major product formed in theses reactions is the branched product **B**, with a ratio **B**/**L** of 98/2 (Table 2).

With ketones the yields are good to excellent and do not seem to greatly depend on the nature of the butenyl acetate (crotyl or its isomer) (Table 2, entries 1−4, 6, and 7). So, crotyl acetate and 1-methyl prop-2-enyl acetate have the same efficiency in this coupling reaction: same yield, and same **B**/**L** ratio.

We also applied this procedure to aldehydes (Table 2, entries 11 and 12). Here again, aldehydes are slightly more reactive than ketones. Therefore, the slow addition of the aldehyde to the reaction mixture was used to avoid the direct reductive coupling of the aldehyde into the corresponding pinacol. Thus, the reaction was conducted with 2 equiv of 1-methyl prop-2-enyl acetate initially in the solution, and an addition of the aldehyde via a syringe pump. Yields are good with this procedure. With aldehydes, the reaction is regiospecific (**B**/**L** = 100/0), since the linear product was not detected.

In the case of dissymmetric carbonyl compounds (Table 2, entries 6−8 and 10−12), we obtained the coupling product, as two couples of diastereoisomers, with moderate diastereoselectivity. The *erythro*/*threo* ratio is about 60/40, depending on the nature of the carbonyl compounds.

It is interesting to note that the coupling is more efficient with crotyl acetate than with allyl acetate.

Results with crotyl chloride are also reported. Better yields were obtained with allylic acetates than with allylic chlorides (Table 2, compare entries 3 and 5, entries 6 and 8), as well as shorter reaction times and less reagent. Nevertheless, the regioreactivity and the stereoselectivity are identical (same **B**/**L** and *erythro*/*threo* ratio).

Allylic chlorides are more reactive toward electrogenerated Fe^{I} than allylic acetates, so the dimerization of this compound occurs preferentially instead of the coupling reactions.

We finally applied the reaction to other allylic compounds: cynnamyl and prenyl acetate. Cross-coupling product is obtained in good yield and high regioselectivity with use of only 1 equiv of cynnamyl acetate (Table 2, entry 13). Prenyl acetate is a poor reagent, since products were obtained with lower yields (<50%) (Table 2, entries 14 and 15). This may be due to the occurrence of steric hindrance in the branched product obtained more with prenyl acetate than with other allylic compounds. Here again, no linear isomer was detected.

Conclusion

We have reported in this paper an original method of efficient cross-coupling of allylic acetates with carbonyls compounds, enabling the preparation of valuable target molecules: homoallylic alcohols. The method is efficient with aldehydes as well as with ketones. The efficiency of iron salts in this process has been clearly demonstrated. The method is also very easy, cheap, and nontoxic, compared to the other methods described in the literature, where palladium complexes, in the presence of another reducing salt, must be used to activate allyl acetate. In addition, iron salts are released by oxidation of the anode, thus avoiding the use of $FeBr_2$, which is air and moisture sensitive. The reduction of Fe^{II} at the cathode probably leads to Fe^{I}, which is stabilized by 2,2′-bipyridine, or allyl acetate itself. Reactions are regioselective: the branched product **B** is the major product, and sometimes the only one.

Experimental Section

GC analysis was carried out using a 25-m capillary column. Mass spectra were recorded with a spectrometer coupled to a gas chromatograph. Column chromatography was performed on silica gel 60, 70−230 mesh. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 200 MHz with TMS as an internal standard.

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The electrochemical cell has been described previously.[19]

All solvents and reagents were purchased and used without further purification. DMF and acetonitrile were stored under argon.

2,2′-Bipyridine was used as obtained commercially. NBu_4BF_4 was dried by heating overnight at 70 °C in a vacuum.

Preparation of Allylic Acetate. Crotyl, 1-methyl prop-2-enyl, and prenyl acetates were prepared from the commercially available corresponding alcohols via esterification reaction.[20]

Crotyl acetate (100%): ^{1}H NMR ($CDCl_3$) δ 1.73 (d, J = 5 Hz, 3H), 2.07 (s, 3H), 4.55 (d, J = 5 Hz, 2H), 5.33−6.17 (m, 2H); MS 115 (M + 1, base), 61, 55, 43.

1-Methyl prop-2-enyl acetate (75%): ^{1}H NMR ($CDCl_3$) δ 1.31 (d, J = 6.4 Hz, 3H), 2.06 (s, 3H), 5.13 (dd, J = 10.5, 1.2 Hz, 1H), 5.24 (dd, J = 17.2, 1.2 Hz, 1H), 5.25 (qd, J = 6.4, 5.9 Hz, 1H), 5.85 (ddd, J = 17.2, 10.5, 5.9 Hz, 1H), MS 115 (M + 1, base), 55.

Prenyl acetate (87%): ^{1}H NMR ($CDCl_3$) δ 1.71 (s, 3H), 1.76 (s, 3H), 2.04 (s, 3H), 4.56 (d, J = 7.2 Hz, 2H), 5.35 (t, J = 7.2 Hz, 1H); MS 128 (M), 73, 59 (base).

Allyl and cynnamyl acetate were commercial products.

General Procedure for the Fe(II)-Catalyzed Electrosynthesis. In an undivided cell equipped with a nickel sponge (area 20 cm^2) as the cathode and an iron rod as the anode, under argon, tetrabutylammonium tetrafluoroborate (0.6 mmol) was dissolved as supporting electrolyte in DMF (40 mL). 1,2-Dibromoethane (1.25 mmol) was introduced. A short electrolysis was run at constant current density (0.3 A) and at room temperature within 15 min to generate a small amount of iron ions. Then the current was turned off. 2,2′-Bipyridine (5 mmol), carbonyl compounds (10 mmol), and a portion of the allyl acetate (ca. 0.3 mmol) were added. The excess of allyl acetate was introduced via a syringe pump at a rate of ca. 4 mmol/h. The electrosynthesis was run at constant current density (0.25 A). The reaction was monitored by GC and stopped after carbonyl compounds was consumed (ca. 4.5 h). A charge of 4 F·mol^{-1} was used in most reactions described in this paper. The mixture was then hydrolyzed with 1 N hydrochloric acid and diluted with diethyl ether. The aqueous layer was extracted with diethyl ether, the combined organic layers were washed with water and saturated NaCl solution and dried over $MgSO_4$, and the solvent was evaporated. The oil thus obtained was purified by column chromatography to give the desired compounds.

Chemical Abstracts Registry Numbers, in brackets, supplied by the author: (2-propenyl)-1-cyclohexanol [1123−34-8]; 1-allylcyclohex-2-en-1-ol [65995-76-8]; 2-phenyl-pent-4-en-2-ol [4743-74-2]; 2-[2]thienyl-pent-4-en-2-ol [116021, Beilstein]; 4,8-dimethyl-nona-1,7-dien-4-ol [17920-92-2]; 4-methyl-nona-1-en-4-ol [40674-50-8]; 1-allyl-cyclopentanol [36399-21-0]; 1-dodecen-4-ol [77383-04-1]; 1-phenyl but-3-en-1-ol [936-58-3]; 1-(1-methyl-2-propenyl)-cyclohexanol [36971-11-6]; 1-(but-3-en-2-yl)-cyclopentan-1-ol [52922-26-6]; 2-phenyl-3-methyl-4-penten-2-ol [61967-11-1]; 3-ethyl-4-methyl-hex-5-en-3-ol [25201-42-7]; 2-(2-thienyl)-3-methyl-4-penten-2-ol [128081-10-7]; 2-methyl-1-phenylbut-3-en-1-ol [25201-44-9]; 3-methyl-dodec-1-en-4-ol [114067-39-9]; 1-(1-phenyl-2-propenyl)cyclohexanol [79801-99-3]; 3-ethyl-4,4-dimethyl-hex-5-en-3-ol [55629-20-4]; 1-(1,1-dimethyl-allyl)-cyclohexanol [36971-12-7].

JO026782R

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