Pergamon

Tetrahedron, Vol. 53, No. 17, pp. 6027-6034, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00280-9

Allylation of Carbonyl Compounds in the Presence of Catalytic Electrogenerated Zinc. Unusual Regioselectivity with a Trifluorinated Analog of Prenyl Bromide.

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Abstract : A mild and effective method of electrochemical zinc activation based on the cathodic reduction of a catalytic amount of $ZnBr_2$ in acetonitrile is applied to the coupling of a trifluorinated analog of prenyl bromide with carbonyl compounds and affords unusual regioselectivity.

Introduction

Allylic organometallics are of a great interest in organic synthesis for carbon-carbon bond formation[1-2]. The direct reaction of allylic halides with carbonyl compounds in the presence of metals (without initial preparation of organometallic species) is a versatile method for the synthesis of homoallylic alcohols (the Barbier reaction)[3]. Initial studies focused on the regioselectivity of the reaction of allylic organometals with electrophiles (SE^2, SE'^2). Many metals are used but the low reactivity of zinc species make these reagents compatible with a wide spectrum of functional groups on the organic halide.

Thus, as allylzinc halides show a comparable reactivity with Grignard reagents, organic chemists prefer using these zinc derivatives. However, one of the major drawback related to the use of zinc metal is the preparation of active zinc or other zinc/metal couples. Several procedures have been developped for the activation of zinc : washing zinc with diluted hydrochloric acid [4a], reduction of zinc halide with alkali metals such as Li, K or C_8K [4b-c], ultrasonic irradiation [4d] or the use of Zn/Cu [4e] or Zn/Ag [4f]. These methods require high temperatures and/or long reaction times.

We have recently reported a simple and mild method for zinc activation using an electrochemical process, based on the cathodic reduction of a catalytic amount of zinc bromide in the presence of a zinc anode. This process has been applied to the coupling of electrophiles with α-bromoesters [5a-b], benzylic [5c] and allylic bromides [5d].

In this paper, we explore the transposition of this method to the coupling of a trifluoroprenyl bromide towards carbonyl compounds. The resulting compounds are of great interest in the terpenes synthesis.

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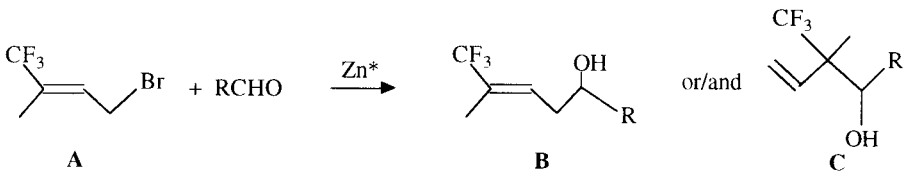
Moreover, the reactivity of the fluorine compounds is different from their hydrogeno analogs. In hydrogeno series, the coupling of allylzinc halides with aldehydes or ketones (except phenyltriisopropylsilyl-ketone), always leads to transposition products [6]. It is also well known that prenyl zinc bromide reacts with aldehyde at the γ position.

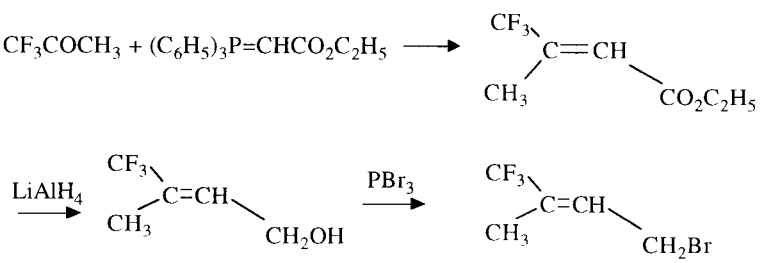
However, in the case of the trifluoroprenyl bromide A, transposition C or non transposition B products are obtained depending on the nature of the aldehyde (Scheme 1).



Scheme 1

Preparation of the trifluorinated prenyl bromide:

This compound was prepared as described[7], starting from trifluoroacetone. The initial Wittig condensation gave ethyl 3-(trifluoromethyl)but-2-enoate as a 95:5 E/Z isomers mixture. The corresponding prenyl alcohol, formed by reduction of this ester with lithium aluminium hydride was also obtained as a mixture of isomers in the same ratio. Treatment of this alcohol with phosphorus tribromide gave 1-bromo-3-(trifluoromethyl)but-2-ene isolated as a 96:4 E/Z isomers mixture (scheme 2).

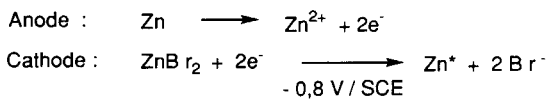


Scheme 2

Results and discussion

1/ Allylation of aldehydes with trifluoroprenyl bromide A.

The activated zinc was prepared by electroreduction of an anhydrous $ZnBr_2$ amount in acetonitrile solution containing tetrabutylammonium tetrafluoroborate as supporting electrolyte. The reaction takes place in a single compartment cell fitted with a commercial zinc rod as an anode and a zinc sheet or a gold gauze as a cathode. At a constant intensity of 0,1 A (cathode potential = - 0,8 vs SCE), 200 coulombs were passed through the solution, at room temperature, corresponding to the 2 e^- reduction of c.a. 1 mmol. of $ZnBr_2$. The reaction occuring at the electrodes can be expressed as follows :



When a gold cathode is used, a grey zinc deposit at the cathode is observed referred to as Zn*. Next, the carbonyl compound (4 mmoles) and trifluoroprenyl bromide (5 mmoles) were added in the solution. The zinc deposit disappear instantaneously to form probably an organozinc species.Without further electrolysis, the coupling product is obtained with good yield. The zinc metal present in the solution (in the form of anode and cathode) is chemically consummated, indicating that it is responsible for the reductive coupling. It can be noticed that a short electrolysis increases the rate of the reaction, and that the coupling does not occur without electrodeposited zinc in catalytic amount. Several examples of addition to aldehydes are mentioned in table 1.

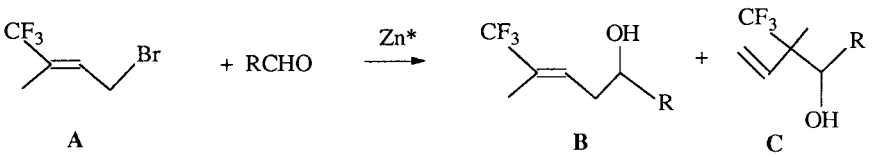
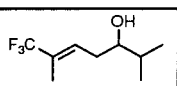
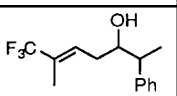
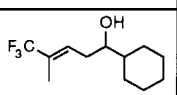
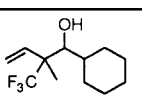
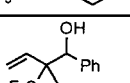
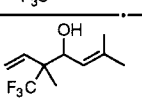
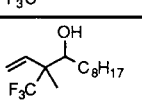


Table 1

Entry (n°of product)	RCHO	Product B (α allylation)	Product C (γ allylation)	Yield %
1			-	13
2			-	46
3				63
4	Ph–CHO	-		70
5		-		57
6	$C_8H_{17}CHO$	-		79

Except in the case of isobutyraldehyde (entry 1), where the non optimized poor yield may be due to the high volatility of the resulting product, the alcohols are formed in good yields. However, the regioselectivity depends on the nature of the aldehyde. When the aldehyde is sterically hindered (entries 1-2), α allylation is observed. Inversely, (entries 4-5-6), branched alcohols (γ allylation) result from non hindered or aromatic aldehydes. In all cases, no pinacols are formed. From cyclohexane carboxaldehyde (entry 3), α and γ products are obtained respectively in a 65:35 ratio. Starting from 3-methyl-2-butenal (entry 5) a fluorinated analog of (±) artemisia alcohol [8] is formed in one-step.

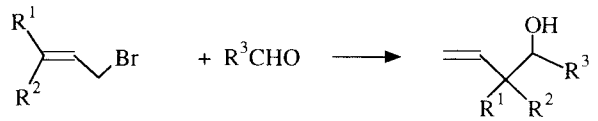
To our knowledge, no zinc derivative of the trifuoroprenyl bromide has been reported. Therefore, an experimental aimed to form this allylic zinc by a chemical method with usual zinc was attempted but the result was not conclusing[9].

In order to compare our results with the hydrogeno series, we have carried out the same electrochemical method with various aldehydes and usual allyl bromides.

2/ Allylation of aldehydes with usual allyl halides.

The coupling of allylic bromides with carbonyl compound has been described in our laboratory only with crotyl bromide[5d]. In that case, the ratio of branched to linear alcohol was always 95:5 or higher.

The coupling reaction is represented as follows (scheme 3).



Scheme 3

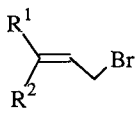
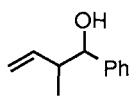
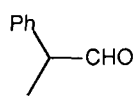
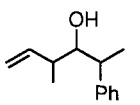
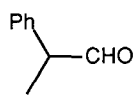
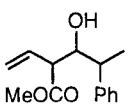
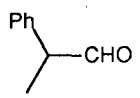
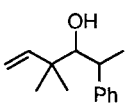
The experimental conditions were the same than those described above. Results are gathered in table 2.

When the aldehyde is non hindered (entry 7), γ allylation always occurs in good yields. Contrary to fluorine series (entry 2), when a hindered aldehyde is used (entry 10), γ allylation is observed, showing that the CF_3 group plays an important role.

We have attempted to change the nature of the group borne by the allylic double bond. In spite of the presence of an electron withdrawing group on the allylic bromide, the transposition product is also obtained (entry 9). The presence of one or two donnor groups do not change the resulting product (γ allylation) (entries 8 and 10). So, the effect of CF_3 is double, as it provides both an electronic effect and a steric effect.

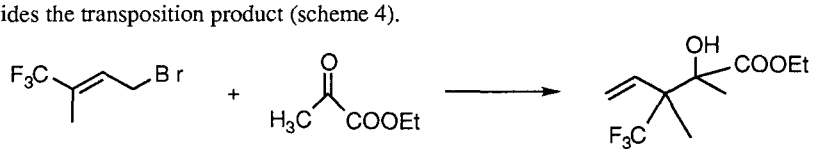
We have also studied the coupling reaction of trifluoroprenyl bromide with various carbonyl compounds as in the hydrogeno series.

Table 2

Entry (n°of product)			R^3CHO	Product	Yield %
	R^1	R^2			
7	CH_3	H	Ph—CHO		80
8	CH_3	H			73
9	CH_3OCO	H			59
10	CH_3	CH_3			40

3/ Coupling of the trifluoroprenyl bromide A with other carbonyl compounds.

Allylic zinc bromides also generally couple with ketones and acid anhydrides. In the case of the trifluoroprenyl bromide A, our attempts were successfull only with ethyl pyruvate. However, it appears that this reaction provides the transposition product (scheme 4).



A 11 Yield 50%

Scheme 4

Conclusion

In acetonitrile, the electroreduction of a catalytic amount of $ZnBr_2$ allows the formation of an active zinc deposit, which induces the formation of an organometallic zinc compound from the trifluoroprenyl bromide A.

Zinc metal arising from the anode and/or the cathode promotes the reductive coupling with aldehydes and ethyl pyruvate.

The formation of the transposition product depends on the nature of the carbonyl compound. When the aldehyde is sterically hindered, α allylation occurs and inversely, when the aldehyde is not hindered, γ allylation is observed.

Our results are far different from the hydrogeno series. In the latter case, γ allylation always occurs. In the fluorine series, a steric effect and probably an electronic effect can explain this difference. No reaction takes place with ketones and acid anhydrides contrary to the hydrogeno series.

This method is an efficient alternative to synthesize terpene analogs by virtue of the mildness of the reaction conditions and the high regioselectivity. Moreover, the reaction is carried out in a one step procedure.

Experimental

General procedure : The three electrode single-compartment electrochemical cell was similar to that described previously[10]. The anode was a cylindrical rod of zinc (diameter 1.3 cm) surrounded by a gold gauze or zinc sheet cathode (apparent surface 40 cm^2). A solution of acetonitrile (40 ml) of $ZnBr_2$ (2mmol) containing $nBu_4N^+BF_4^-$ (0.1 mmol) was electrolyzed under argon until 200 Coulombs had passed, either at i = 100mA or at E = -0.8 V vs SCE. Once the electrolysis was stopped, the carbonyl compound (4 mmol) and the allylic bromide (5 mmol) were added and the solution stirred at room temperature. To accelerate the reaction, a few amount of electricity is necessary (about 200 C). The reaction was followed by GC until disappearance of the halide (0.5 hours). The solution was hydrolyzed with 0.1 N HCl and extracted with ether, the organic layer washed with water, dried and the solvent evaporated. The products were purified by flash column chromatography on silicagel with pentane/ether mixtures as eluent. The compounds were analyzed by NMR (^1H, ^{13}C and ^{19}F), IR and mass spectrum. Precises mass determinations or microanalysis were not obtained because these homoallylic alcohols are not time stable and must be used just after synthesis. Products purity has been estimated from ^1H, ^{19}F NMR and GC data.

Product analysis: ^1H NMR (δ, ppm from TMS), ^{13}C NMR (δ, ppm from TMS) and ^{19}F (δ, ppm from $CFCl_3$), spectra were obtained from AC 200 Bruker spectrometer ($CDCl_3$ solution) mass spectra were mesured on a Finnigan. GC MTI 800 spectrometer, IR spectra were obtained on a Perkin Elmer 283B spectrophotometer.

- 7,7,7-trifluoro-2,6-dimethylhept-5-en-3-ol (**1**) purum: 97%; ^1H NMR: 6.19 (m,1H); 3.48 (dt,1H,J=5.1, 7.5 Hz); 2.27 (m,2H); 1.8 (s,3H); 1.69 (quint,1H,J=6.7Hz); 0.95 (d,6H,J=6.7Hz). ^{13}C NMR: 10.76; 17.02; 18.69; 32.24; 33.42; 75.78; 123.5 (q, J=280Hz); 127 (q, J=30Hz); 130.5 (q,J=6Hz) ^{19}F NMR: -69.8. Mass m/e: 179 (M-OH); 159 (M-OH-HF); 137 (M-OH-C_3H_6); 73 (C_4H_9O) 100%; 104 ($C_5H_6F_2$)

- 7,7,7-trifluoro-6-methyl-2-phenylhept-5-en-3-ol (**2**) purum: 95%; ^1H NMR: 7.12 - 7.33 (m,5H); 6.13 (t,1H,J=6.9Hz); 3.7 (m,1H); 2.7 (m,1H); 2.1 (m,2H); 2 (m,1H); 1.62 (s,3H); 1.31 (d,3H). ^{13}C NMR:

10.51; 16.44; 17.49; 32.8; 45.66; 75.32; 126.5; 126.7; 127.5; 128.44; 143.91.^{19}F NMR: - 69.2. Mass m/e: 241 (M-OH); 135 (M-H_2O-C_8H_9); 106 (C_8H_{10}) 100%. IR (neat): 3490, 1730, 1690, 1460, 910, 760, 700.

- 1-cyclohexyl-5,5,5-trifluoro-4-methylpent-3-en-1-ol (**3a**) and 1-cyclohexyl-2-methyl-2-(trifluoromethyl)but-3-en-1-ol (**3b**) purum: 97%; ^{1}H NMR: 6.2 (t,1H)^{3a}; 5.87 (dd,1H,J=17 Hz;10 Hz)^{3b}; 5.37 (d,1H,J=10Hz)^{3b}; 5.33 (d, 1H, J=17Hz)^{3b}; 4.2 (m,1H)3b; 3.4 (q,1H)^{3a}; 3.2 (s,OH); 2.3 (m,2H)^{3b}; 1.8 (s,3H)^{3a}; 1.7-1.0 (m, 14H)$^{3a-b}$. 19F NMR: - 72.3; -72.5 (2 diastereoisomers 65/35 CF_3-C*-); - 69.2; -69.5 (2 isomeres 90/10 CF3-=-). Mass m/e: 219 (M-OH); 199 (M-OH-HF); 177 (M-C_3H_7O); 163 (M-C_4H_90); 95 (C_7H_{11}) 100%. All isomeres present similar M.S. IR (neat): 3490, 1720, 1690, 1460, 910, 760, 700.

- 2-methyl-1-phenyl-2-(trifluoromethyl)but-3-en-1-ol (**4**) purum: 93%; ^{1}H NMR : 7.24 (s,5H); 6.23 (dd,1H,J=10.9 Hz); 5.38 (d,1H,J=10.9 Hz); 5.11 (d,1H,J=17.7 Hz); 4.85 (s,1H);2.75 (sl,OH); 0.97 (s,3H). ^{13}C NMR: 14.18; 51.3 (q,J_{CF}=22.3 Hz); 75.49; 119.9; 127.42; 127.59; 127.97; 128.08; 127.6 (q,J=284 Hz); 136.1; 139.34. ^{19}F NMR: - 71.4 (80%); - 71 (20%). Mass m/e: 213 (M-OH); 193 (M-OH-HF); 173 (M-OH-2HF); 107 (C_7H_7O) 100% . IR (neat): 3460, 1720, 1650, 1460, 940, 700.

- 3-dimethyl-3-(trifluoromethyl)hepta-1,5-dien-4-ol (**5**) 2 diastereoisomeres 50/50 show identical spectra purum: 97%; ^{1}H NMR: 6.10 and 5.82 (2dd,1H,J=11, 17.5 Hz); 5.36 (m,2H); 5.15 (m,1H); 4.53 (m,1H); 1.94 (m,OH); 1.74 (2d,6H); 1.31 - 1.13 (2s,3H). ^{13} C NMR: 12.87; 13.48; 18.13; 25.78: 58.87 (q,J=22 Hz); 69.6; 118.48; 119.3; 122.18; 122.45; 127.6 (q, J = 284.3Hz); 133.43; 133.7; 137.46; 137.83. ^{19}F NMR : - 71.8. Mass m/e: 177 (M-CH_3O); 149 (M-$CH_3$0-C_2H_4); 123 (M-CH_3O-C_4H_6); 103 (M-CH_3O-C_4H_6-HF); Mass CI: 227 ($M^+H_3O^+$).IR (neat): 3460, 1680, 1650, 1470, 1420, 1385, 1280, 1090, 1000, 940, 850, 725.

- 3-methyl -3-(trifluoromethyl)dodec-1-en-4-ol (**6**) purum: 92%; ^{1}H NMR: 5.79 (dd,1H,J=11Hz and 20.3 Hz); 5.37 (2d, 2H,J = 8.7 and 17.4 Hz); 3.8 (m, 1H); 2.02 (d,OH); 1.6- 1.2 (m, 16H); 0.88 (t, 3H). ^{13}C NMR: 11.48; 13.81; 22.46; 26.39; 29.1; 29.26; 29.39; 31.53; 31.68; 51.12 (q,J=21.3 Hz); 72.83; 116.5; 128 (q,J=284.5 Hz); 134.33. ^{19}F NMR: - 71.4. Mass CI: 248 (M-H_2O); 193 (M-H_2O-C_4H_7); 179 (M-H_2O-CF_3); 165 (M-H_2O-C_6H_{11}); 143 ($C_9H_{19}O$); 69 (CF_3).IR (neat): 3460, 1680, 1650, 1470, 1420, 1385, 1280, 1090, 1000, 940, 850, 720

- 2-methyl-1-phenyl but-3-en-1-ol (**7**) [11]

- 4-methyl-2-phenyl hex-5-en-3-ol (**8**) [12]

-methyl 2-(1-hydroxy-2-phenylpropyl)but-3 enoate (**9**) purum: 85%; ^{1}H NMR:7.4-7.1 (m,5H); 6.1-5.8 (m,1H); 5.4-5.0 (m,2H); 3.8-3.65 (m,4H); 2.7-3.3 (m,2H); 1.33 (d,3H).^{13}C NMR: 13.75; 14.22; 17.91; 18.34; 42.35; 43.1; 45.4; 51.51; 51.72; 51.81; 52.88; 53.45; 54.06; 73.75; 75.42; 76.62; 118.82; 120.33; 126.41; 126.48; 127.74; 128.02; 128.08; 128.29; 128.36; 128.48; 128.85; 131.2; 133.26; 140.08; 143.91; 144.42; 173.47; 174.03.Mass m/e: 217 (M-OH); 157 (M-H_2O-$COOCH_3$); 129 (M-H_2O-$COOCH_3$-C_2H_8); 105 (C_8H_9); 69 (C_5H_9)100%.IR (neat): 3500,1735, 1640, 1620, 1460, 1020, 980, 910.

- 4,4-dimethyl-2-phenylhex-5-en-3-ol (**10**) purum: 95%; ^{1}H NMR: 7.14-7.29 (m,5H); 5.94 and 5.85 (2d,1H,J=10.2 and 18.1 Hz); 5.0-5.09 (m,2H); 3.5 (d,1H); 3 (m,1H); 1.6 (s,OH); 1.27 (d,3H); 1.05 (s,3H); 1 (s,3H).^{13}C NMR: 16.72; 23.61; 24.66; 41.22; 42.61; 81.79; 112.55; 126.06; 127.58; 128.44; 145.51; 147.8.Mass m/e: 187(M-OH); 135(M-OH-C_9H_{10}); 105(C_8H_9); 70(C_5H_{10}) 100%.IR (neat): 3500, 1640, 1620, 1460, 1020, 980, 910, 760, 700.

- Ethyl 2-hydroxy -2,3-dimethyl-3-(trifluoromethyl)pent-4-enoate (**11**) purum: 93%; ^{1}H NMR: 6.22 (dd,1H,J=10.9 and 17.5 Hz); 5.49 (d,1H,J=10.9 Hz); 5.38 (d,1H,J=17.6 Hz); 4.4 (sl,OH) ; 4.27 (q,2H); 1.39 (s, 6H); 1.32 (t,3H). ^{13}C NMR : 13.7; 21.9; 26.8; 53.5 (q,J=22.4 Hz); 62.54; 75.9; 119.64; 127.2 (q,J=284Hz); 133.38; 174.66. ^{19}F NMR : - 70.12. Mass m/e: 223 (M-H_2O); 167 (M-H_2O-$CO_2C_2H_5$); 147 (M-H_2O-$CO_2C_2H_5$-HF); 117 ($C_5H_9O_3$) 100%. IR (neat): 3460, 1735, 1640, 1620, 1460, 1020, 980, 910.

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(*Received in Belgium* 19 *February* 1996; *accepted* 13 *March* 1997)