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A New Method for the Preparation of 2-Aryl Propionic Acids Using Low-Valent Titanium

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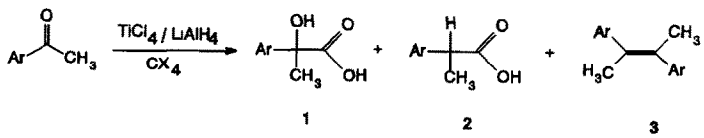
Abstract: The addition of dihalocarbenes to arylmethylketones in the presence of low-valent titanium yields 2-aryl propionic acids in acceptable yield by one pot reaction. The reaction conditions were optimized. The $TiCl_4/LiAlH_4$ ratio is one variable that controls the selectivity of the process.

The 2-aryl propionic acids (Naproxen, Ibuprofen, Ketoprofen, etc.) have interesting pharmaceutical properties as non steroidal antiinflammatory drugs.[1] Recently we have reported a new and simple synthetic methodology to prepare these compounds, by one pot reaction.[2] In the present paper we report a new methodology to obtain these acids generating the dihalocarbene using low-valent titanium.[3] The reduced titanium produced in this process is very efficent in the generation of dihalocarbenes. However, unfortunately, would seem to have no potential for the effective generation of monohalocarbenes (CHX:).[4] Originally the 2-hydroxy acid **1** was expected as the reaction product. Nevertheless, initial exploratory reactions of $CFCl_3$ with *p-iso*-butyl acetophenone in presence of low valent titanium (Table 1) gave 2-*p-iso*-buthylphenyl propionic acid with good yields depending on the molar ratio of reagents ($TiCl_4/LiAlH_4$) used to generate the low-valent titanium (Scheme 1).

Scheme 1



1 **2** **3**

We can observe in Table 1 the dramatic effect on selectivity of the molar ratio $TiCl_4/LiAlH_4$. An excess of $LiAlH_4$ favours the synthesis of the carboxylic acid. The optimum conditions were between 1/2.5 and 1/3. This fact could be explained because an excess of $LiAlH_4$ decreases the generation of the titanium complex that favours the reductive coupling of the ketone to produce the olefin **3**, and the hydrogenolysis of the intermediate 2-hydroxy acid **1**. The reaction temperature range between -5°C and 0°C is necessary to minimize the carbonyl-coupling reactions.

Table 1

Product balance[a] by addition of chlorofluoro-carbene to *p-iso*-butyl acetophenone as a function of the molar ratio of $TiCl_4$ to $LiAlH_4$.[b]

$TiCl_4/LiAlH_4$ molar ratio	% carboxylic acid	% hydroxy acid	% olefin
1/0.5	12	36	40
1/1	20	35	35
1/2	46	32	20
1/2.5	67	10	5
1/3	62	0	5

a) Yields determined by integration of the reaction mixture ^{1}H-RMN spectrum.

b) The reaction conditions were 1 hour at -5° C. See the text for further experimental conditions

Table 2

(R,S)-2-aryl-propionic acid yields obtained from the addition of cholorofluorocarbene several arylmethylketones.

Ar	Yield (%)[a]	Yield (%)[b]
C_6H_5	78	65
p-ClC_6H_4	70	60
p-MeC_6H_4	68	58
p-iso-$C_4H_9C_6H_4$	67	60
6-methoxy-2-naphthyl	62	60

a) Determined by integration of the ^{1}H-RMN spectrum of the crude mixture

b) Isolated product

Typical experimental procedure.

A flask containing 150 ml of THF under nitrogen was cooled to -5°C and 9.5 g (0.05 mol) of $TiCl_4$ were carefully added over 20 minutes. A solution of 4.74 g (0.125 mol) $LiAlH_4$ in 30 ml THF was carefully added to the mixture over 30 minutes. The reaction mixture was cooled again, when the temperature had fallen to -5°C, 8.8 g (0.05 mol) of *p-iso*butyl-acetophenone in 50 ml THF were added. Inmediately, 6 g (0.05 mol) of $CFCl_3$ were added to the mixture, and stirred at -5°C for 30 minutes. Then, the mixture was hydrolyzed with HCl diluted and was extracted with ethylic ether. The crude product was purified by flash chromatography, gave 6.2 g (60 %) of (R,S)-2-(*p-iso*-butyl-phenyl)-propionic acid. The racemic nature of the product has been determined by ^{1}H-NMR using 1,2-diphenyl-diaminoethane as chiral agent.[5]

References and Notes

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