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Pinacol Coupling of Aromatic Aldehydes using La-TiCl₄ in CH₃COOEt under Ultrasound Irradiation

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Abstract: Titanium tetrachloride can be reduced by lanthanum filings to the corresponding low valent titanium complex, which can induce some aromatic aldehydes to the corresponding pinacols in 28%-97% yields within 10-50 min in ethyl acetate at r.t. under ultrasound irradiation.

Keywords: Pinacol coupling; aromatic aldehydes; lanthanum; titanium tetrachloride; ultrasound.

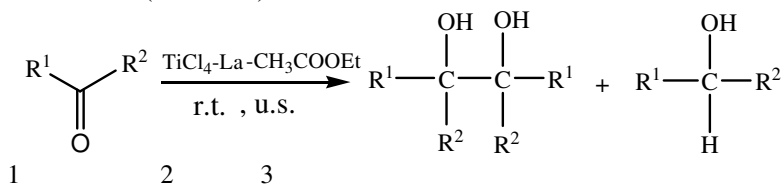
Introduction

One of the most powerful methods for constructing carbon-carbon bond is the reductive coupling of carbonyl compounds giving olefins and/or 1,2-diols. Of these methods, the pinacol coupling, which was described in 1859, is still a useful tool for the synthesis of vicinal diols¹⁻². 1, 2-Diols obtained in the reaction were very useful synthons for a variety of organic synthesis, and were also used as intermediates for the construction of biologically important natural product skeletons and asymmetric ligands for catalytic asymmetric reaction³. In particular, pinacol coupling has been employed as a key step in the construction of HIV-protease inhibitors⁴. Recent efforts have focused on the development of new reagents and reaction systems to improve the reactivity of the reagents and diastereoselectivity of the products.

As reducing reagents, low valent metallic species have a significant role for organic molecules. Among these low valent metallic species, low valent titanium is a highly reactive reagent and increasing attracting in organic sythesis ⁵. The reduction of TiCl₄ to lower valent titanium species and the synthetic utility of such species are well documented chemistry of wide interest ⁶. Many pioneers have reported their efforts in this field. In 1973, Mukaiyama firstly reported that TiCl₄-Zn reduced aromatic aldehydes and ketones to produce the corresponding 1,2-diols in high yield ⁷, but the stereoselectivity was not reported. Following Mukaiyama, Hu *et al.* reported TiCl₄/Al induced the reductive coupling of aldehydes and ketones to form the corresponding pinacols or olefins ⁸. In 1999, Periasamy *et al.* have reported reductive coupling of aromatic aldehydes using TiCl₄/Et₃N to give high diastereoselectivities ⁹. In 2000, Li *et al.* reported the 1,2-diols were obtained in pinacol coupling mediated by TiCl₄-Mg with a high stereoselectivity ¹⁰. In the same year, several other reports described the pinacolization under different systems ¹¹⁻¹². Li *et al.* have used TiCl₄(THF)₂/Zn with tattaic ester or Schiff base to mediate pinacol coupling reaction in high yields, excellent diastereoselectivities and good enantioselectivities ¹³⁻¹⁴. However, in spite of their potential utility, some of the reported methods suffer from drawbacks.

Ultrasound has increasingly been used in organic synthesis in the last three decades. A large number of organic reactions, especially many metal-involved reactions, can be carried out in higher yields, shorter reaction time and milder conditions under ultrasound irradiation ¹⁵. Lim *et al.* reported the reaction of aromatic aldehydes with indium using sonication affording the corresponding diols in moderate to good yields ¹⁶; Basu *et al.* reported the reduction of several aromatic ketones to diols by samarium-ammonium chloride under sonication at room temperature, and the reaction could be completed within 5 min ¹⁷. Mecarova and Toma reported the pinacol coupling reaction in aqueous media under ultrasound irradiation and found that ultrasound considerably accelerates the benzaldehyde's conversion ¹⁵.

Metal lanthanum has strong reducing power (La³⁺/La = -2.362 V) similar to that of magnesium (Mg²⁺/Mg = -2.37 V). The rare metals mediated the pinacolization of aromatic aldehydes have been reported ¹⁶⁻¹⁸. To the best of our knowledge, there were no literature examples of pinacol coupling of aromatic aldehydes and ketones using La-TiCl₄ in ethyl acetate under ultrasound. Recently, our laboratory has also reported the pinacolization mediated by TiCl₄-M systems under ultrasound irradiation ¹⁹. In order to study the influence of different reductive metals on the reaction, we wish to study the possibility of the pinacol coupling of aromatic aldehydes and ketones mediated by La-TiCl₄ in ethyl acetate under ultrasound irradiation (Scheme 1).



Scheme 1 Pinacolization of the aromatic aldehydes under ultrasound irradiation

Experimental

Materials and Measurements

Liquid aldehydes and CH_3COOEt were distilled prior to use. IR spectra were recorded on a Bio-Rad FTS-40 spectrometer (KBr). Elemental analysis was measured on a HERAEUS (CHNO, Rapid) analyzer. MS were determined on a VG-7070E spectrometer (EI, 70 eV). ^1H NMR spectra were measured on a Bruker AVANCE 400 (400 MHz) spectrometer using TMS as the internal standard and CDCl_3 as a solvent. Sonication was performed in Shanghai Branson-CQX ultrasonic cleaner (with a frequency of 25 kHz and a nominal power 250 W) and SK 250 LH ultrasonic cleaner (with a frequency of 40 kHz, 59 kHz and a nominal power 250 W; Shanghai Kudos Ultrasonic Instrument Co., Ltd.). The reaction flask was located in the maximum energy area in the cleaner bath, where the surface of reactants is slightly lower than the level of the water. The reaction temperature was controlled by addition or removal of water from ultrasonic bath.

General Procedure

A 50 mL two-neck round flask was charged with anhydrous MeCOOEt (4 mL) and TiCl_4 (2 mmol) under a nitrogen atmosphere. And then the flask was located in the cleaner bath. After one minute of irradiation, La filings (4 mmol) were added in one portion. When the reaction mixture turned into dark-blue color, a solution of the desired aldehyde or ketones (**1**, 1 mmol) in 1 mL MeCOOEt was added. The mixture was irradiated for a period as indicated in Table 1 (the reaction was monitored by TLC). After the completion of the reaction, the resulting suspension was extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with saturated aqueous NaHCO_3 solution and brine, dried over anhydrous magnesium sulfate for 12 h and filtered. Ethyl acetate was evaporated under reduced pressure to give the crude product, which was separated by column chromatography on silica (200-300 mesh), eluted with petroleum ether or a mixture of petroleum ether and diethyl ether. The authenticity of the product was established by their ^1H NMR, IR, MS, or/and elemental analysis data.

2a ^1H NMR: δ 4.69 (2H, s, CH, *dl*), 4.83 (2H, s, CH, *meso*), 7.11-7.32 (20H, m, Ph-H) ppm. *m/z* (%): 214(1), 180 (7.6), 167 (12.5), 149 (6.0), 107 (93.8), 79 (100), 77 (73.8). IR (KBr) ν_{max} : 3200-3480 cm^{-1} .

2b ^1H NMR: 4.61 (2H, s, CH, *dl*), 4.84 (2H, s, CH, *meso*), 7.02-7.29 (16H, m, Ph-H) ppm. *m/z* (%): 276 (14), 249 (32), 155 (100), 111 (8). IR (KBr) ν_{max} : 3380-3420 cm^{-1} .

2c ^1H NMR: 4.55 (2H, s, CH, *dl*), 4.74 (2H, s, CH, *meso*), 6.85-7.28 ((16H, m, Ph-H) ppm. *m/z* (%): 263 (1.2), 251 (1.6), 178 (4.6), 165 (4.6), 141 (100), 113 (23.8), 77 (71.0). IR (KBr) ν_{max} : 3260-3318 cm^{-1} .

2d ^1H NMR: 5.20 (2H, s, CH, *dl*), 5.50 (2H, s, CH, *meso*), 7.14-7.28 (12H, m, Ph-H) ppm. *m/z* (%) : 352 (1), 305 (1.4), 233 (10), 175 (100), 145 (10), 111 (25), 77 (15). IR (KBr) ν_{max} : 3320~3400 cm^{-1} .

2e ^1H NMR: 5.35 (2H, s, CH, *dl*), 5.60 (2H, s, CH, *meso*), 7.16-7.29 (16H, m, Ph-H) ppm. *m/z* (%): 282 (1), 165 (47), 141 (89), 113 (13), 107 (14), 77 (100), 51 (38). IR (KBr) ν_{max} : 3100~3500 cm^{-1} .

2f ^1H NMR: δ 3.78 (6H, s, CH_3O , *dl*), 3.82 (6H, s, CH_3O , *meso*), 4.63 (2H, s, CH, *dl*), 4.75 (2H, s, CH, *meso*), 6.77-7.06 (16H, m, Ph-H) ppm. *m/z* (%): 276 (14), 249 (32), 155 (100), 111 (8). IR (KBr) ν_{max} : 3300-3600 cm^{-1} .

2g ^1H NMR: δ 4.58 (2H, s, CH, *dl*), 4.67 (2H, s, CH, *meso*), 5.94 (4H, s, CH_2 , *dl*), 5.98 (4H, s, CH_2 , *meso*), 6.58-6.88 (12 m, Ph-H) ppm. m/z (%): 302 (1), 284 (2.5), 268 (5.0), 255 (11.8), 151 (100), 123 (32), 93 (77.1), 65 (39.0). IR (KBr) ν_{max} : 3100-3600 cm^{-1} .

2h ^1H NMR: 4.63 (2H, s, CH, *dl*), 4.84 (2H, s, CH, *meso*), 6.98-7.45 (16H, m, Ph-H) ppm. Anal. calcd. for $\text{C}_{14}\text{H}_{12}\text{O}_2\text{Br}_2$: C 45.16, H 3.23; found C 45.19, H 3.24. IR (KBr) ν_{max} : 3100~3600 cm^{-1} .

2i ^1H NMR: δ 2.33 (6H, s, CH_3 , *dl*), 2.37 (6H, s, CH_3 , *meso*), 4.69 (2H, s, CH, *dl*), 4.77 (2H, s, CH, *meso*), 7.04-7.17 (16H, m, Ph-H) ppm. m/z (%): 242 (1.2), 195 (6), 121 (100), 107 (12), 77 (13). IR (KBr) ν_{max} : 3280-3450 cm^{-1} .

2j ^1H NMR: 4.61 (2H, s, CH, *dl*), 4.78 (2H, s, CH, *meso*), 6.94-7.42 (16H, m, Ph-H) ppm. m/z (%): 325 (6), 186 (16), 157 (8), 107 (7), 77 (100), 51 (13), IR (KBr) ν_{max} : 3200~3500 cm^{-1} .

2k ^1H NMR: δ 1.54 (6H, s, CH_3 , *dl*), 1.62 (6H, s, CH_3 , *meso*), 7.24-7.29 (20H, m, Ph-H) ppm. m/z (%): 225 (4), 206 (4), 181 (32), 165 (9), 121 (100), 105 (12), 77 (11), 43 (80). IR (KBr) ν_{max} : 3100-3600 cm^{-1} .

2l ^1H NMR: δ 4.31, 4.32 (2H, d, CH-O, *dl*), 4.46, 4.47 (2H, d, CH-O, *meso*), 6.27, 6.29, 6.30, 6.31 (2H, dd, =CH), 6.75, 6.78 (2H, d, Ph-CH=), 7.26-7.43 (20H, m, Ph-H) ppm. m/z (%): 264 (1), 248 (6.2), 232(3.6), 219 (3.0), 157 (6.7), 134 (21.4), 133 (100), 115 (24.7), 91 (27.8), 77 (19.9), 55 (37.0). IR (KBr) ν_{max} : 3300-3380 cm^{-1} .

Results and Discussion

From the results in Table 1, it was found that when the amount of PhCHO was 1 mmol, changing the molar ratio of TiCl_4/La has effected the yield of pinacol. When the molar ratio of TiCl_4/La was 2:4, the yield of 1,2-diphenyl-1,2-ethanediol was 73%. Lowering or enhancing the amount of TiCl_4 , the yield of pinacol decreased to 18% and 68% respectively. Similarly, changing the amount of La filings, the yield of pinacol decreased too. The optimum molar ratio of TiCl_4/La was 2:4.

The effect of the ultrasound irradiation frequency and the reaction time on the pinacolization has been also investigated. Increasing the ultrasound irradiation frequency (from 25 kHz to 40 kHz and 59 kHz) has little influenced the yield of pinacol (from 73% to 71% and 71%). When the 4- $\text{ClC}_6\text{H}_4\text{CHO}$ as the substrate, prolong the reaction time from 10 min to 40 min the pinacol yield decreased from 97% to 89%.

We have carried out the experiments in the absence of ultrasound irradiation: the coupling of 4- $\text{ClC}_6\text{H}_3\text{CHO}$ was carried out using stirring in 81% (**2b^a**) yield within 40 min. While under ultrasound irradiation, the corresponding pinacol was given in 97% yield within 10 min. It is obvious that ultrasound irradiation can accelerate the pinacolization. It may be that ultrasonic irradiation can cause La filings rupture, and a decrease in particle size thus increasing the surface area available for reaction¹⁵.

From the above results, a typical general experiment procedure is substrate (1 mmol), TiCl_4 (2 mmol) and La filings (4 mmol) under 25 kHz ultrasound irradiation for a period. We did a series of experiments for pinacol coupling of aromatic aldehydes and ketones under this condition. The results were summarized in Table 1.

Table 1. Pinacol coupling reaction mediated by TiCl₄-La-CH₃COOEt under ultrasound irradiation

Entry	Substrate	Molar ratio of TiCl ₄ /La /substrate	Frequency kHz	Time min	Isolate yield		<i>dl/meso</i> [*]
					2	3	
a	PhCHO	2:3:1	25	40	66	5	—
		2:5:1	25	40	70	14	—
		1:4:1	25	40	18	13	—
		3:4:1	25	40	68	10	—
		2:4:1	25	40	73	13	89/11
		2:4:1	40	40	71	7	—
		2:4:1	59	40	71	10	—
b	4-ClC ₆ H ₄ CHO	2:4:1	25	10	97	1	80/20
		2:4:1	25	40	89	4	—
		2:4:1	stirred	40	81 ^a	9	—
c	3-ClC ₆ H ₄ CHO	2:4:1	25	25	96	1	98/2
d	2,4-Cl ₂ C ₆ H ₃ CHO	2:4:1	25	40	93	5	33/67
e	2-ClC ₆ H ₄ CHO	2:4:1	25	40	64	5	38/62
f	4-CH ₃ OC ₆ H ₄ CHO	2:4:1	25	50	44	9	96/4
g	3,4-(OCH ₂ O)C ₆ H ₃ CHO	2:4:1	25	30	31	8	89/11
h	4-BrC ₆ H ₄ CHO	2:4:1	25	40	88	5	55/45
i	4-CH ₃ C ₆ H ₄ CHO	2:4:1	25	40	28	7	95/5
j	3-BrC ₆ H ₄ CHO	2:4:1	25	30	55	—	97/3
k	PhCOCH ₃	2:4:1	25	50	24	4	47/53
l	PhCH=CHCHO	2:4:1	25	45	39	16	95/5
m	cyclohexanone	2:4:1	25	50	trace	—	—

^{*} Ratio of *dl/meso* was calculated by ¹H NMR.

^a 4-ClC₆H₄CHO as the substrate, the ultrasound irradiation is absent.

The data in Table 1 indicated that some aromatic aldehydes, especially the aromatic aldehydes with electron-withdrawing group can be given high yield of pinacol. But the aromatic aldehydes with electron-donating group have shown lower reactivity (Entry **1f**, **1g**, and **1i**). In the presence process, the pinacol coupling of PhCOCH₃ gave pinacol in 24% yield (Entry **1k**), but other ketones, such as cyclohexanone, 4-ClC₆H₃COCH₃ and PhCOPh, were inert under the reaction conditions. The reason may be the steric hinderance around the carbonyl group inhibits the coupling reaction.

The pinacol coupling reaction can form *dl* and *meso* stereomers. Improved diastereoselectivity has been observed in present system. Most of the aromatic aldehydes gave higher *dl* stereoisomers. Especially, the ratio of *dl/meso* of **2c**, **2f**, **2i**, **2j** and **2l** reached 98/2, 96/4, 95/5, 97/3, 95/5. But some aldehydes (**2d**, **2e**, **2h**) showed lower ratio of *dl/meso*.

Compared to the other system, the ratio of *dl/meso* of the pinacol was improved. When the **1a**, **1c**, **1f**, **1i**, **1l** as the substrates, the ratio of *dl/meso* of pinacol was nearly 9:1-49:1, but in TiCl₄-Mg-CH₃COOEt system¹⁹ the ratio were only 1:1-3:1.

Conclusion

We have found an efficient and convenient method for the preparation of pinacols from some aromatic aldehydes by using La-TiCl₄ in CH₃COOEt under ultrasound irradiation.

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