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Synthesis of Chiral Tricarbonylchromium(0) Aromatic Aldehydes and Their Asymmetric Aldol Reaction with Acetone

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The preparation of chiral tricarbonylchromium(0) aromatic aldehydes was improved in a shorter total time with higher yields comparing with previous methods. Their asymmetric aldol reactions with acetone were studied at room temperature.

Key Words: Synthesis, Asymmetric, Aldol reaction, Tricarbonylchromium(0).

INTRODUCTION

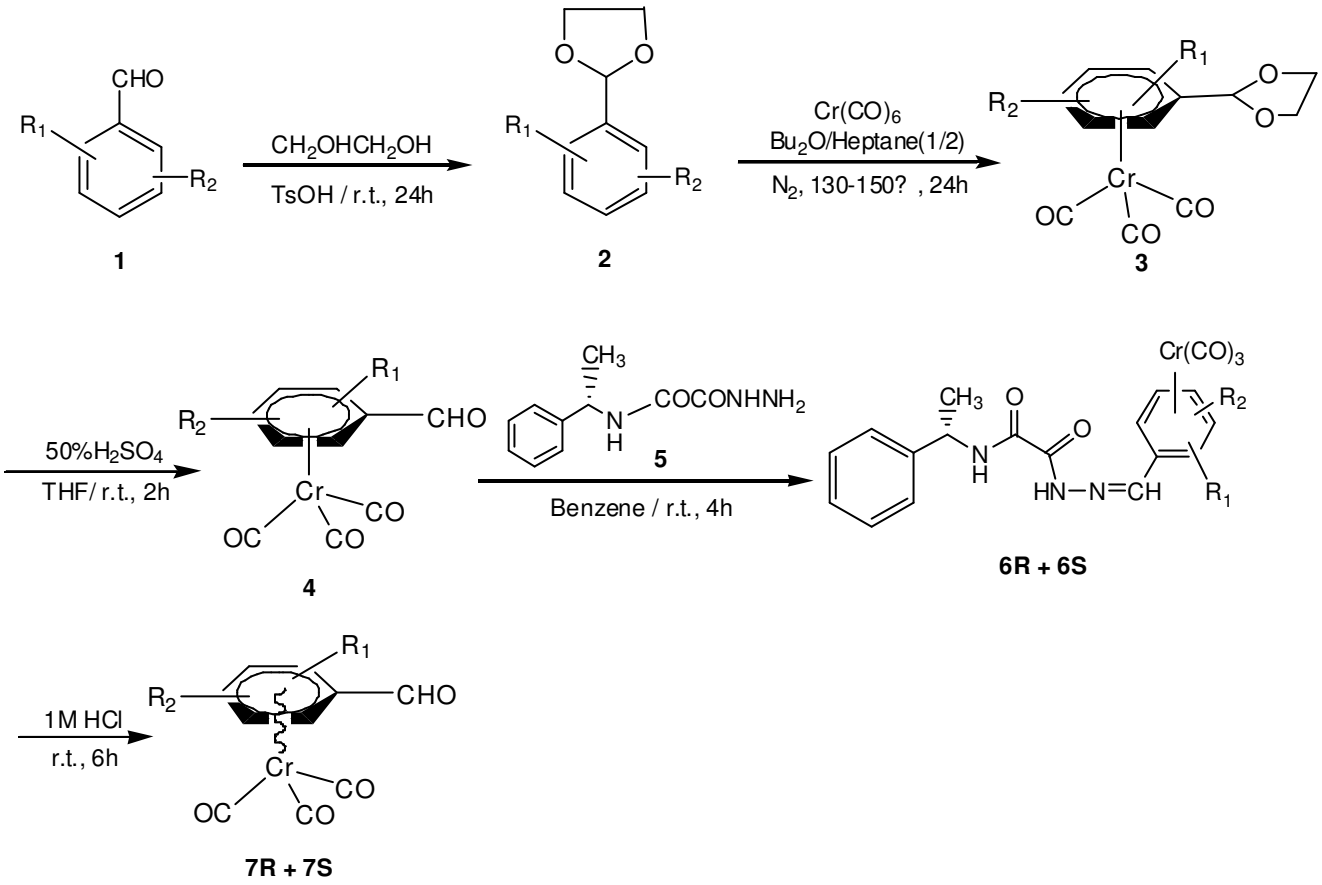
Since the first report about the synthesis of chiral tricarbonylchromium(0) aromatic aldehydes by Sollade and co-workers[1], a number of studies were carried out in order to explore the utility of it. By virtue of its steric bulk, the carbonylchromium group offers complexes to one face of an arene, thus enantiocontrol in asymmetric processes involving organic arene tricarbonylchromium(0) group is usually extremely high. This effect has been utilized recently in enantioselective alkylation[2], allylboration[3], aldol reaction[4] and cycloadditions[5]. Its another benefit is strong electron-withdrawing capacity. The tricarbonylchromium(0) tripod posses a dipole moment[6], which may be exploited by encouraging attractive interactions between it and a substrate in a transition state assembly. It can also allow other substituted groups on aromatic ring react in some abnormal ways, such as the direct facile hydrolysis of aryl halogen without any catalysis in mild condition. Furthermore, the development of chiral auxiliaries for use in enantioselective processes has been widespread over the past few years, reflecting the importance of such facility. The general preparation of chiral tricarbonylchromium(0) aromatic aldehydes was completed in five steps with yield 23 % in 60 h (only taken in reaction, **Scheme-I**: (1) aldehydes **1** were protected with glycol or triethoxy methane to give **2** in boiling volatile and toxic organic solvent (for example, benzene) catalyzed by acids such as TsOH; (2) **2** reacted with $Cr(CO)_6$ at N_2 atmosphere for 24 h to give protected tricarbonylchromium(0) aromatic aldehyde **3**; (3) **3** was deprotected to give the racemic tricarbonylchromium(0) aromatic aldehyde **4**; (4) **4** was resoluted by **5** in benzene for 4 h afforded chiral **6R** and **6S** by column chromatography (**Scheme-II**), respectively; (5) the -CHO of **6R** and **6S** was released in 1M HCl for 6h at room temperature to give chiral **7R** and **7S**, respectively. This classic procedure made it possible to transform a non-chiral aromatic aldehyde to a chiral one, but some shortcoming limited its development and scope, such as long time, using of boiling volatile and toxic organic solvent, especially, the danger of the losing of tricarbonylchromium(0) caused by the long time. Generally, hydrochloric acid and ethanol made **4** unstably in the last step.

EXPERIMENTAL

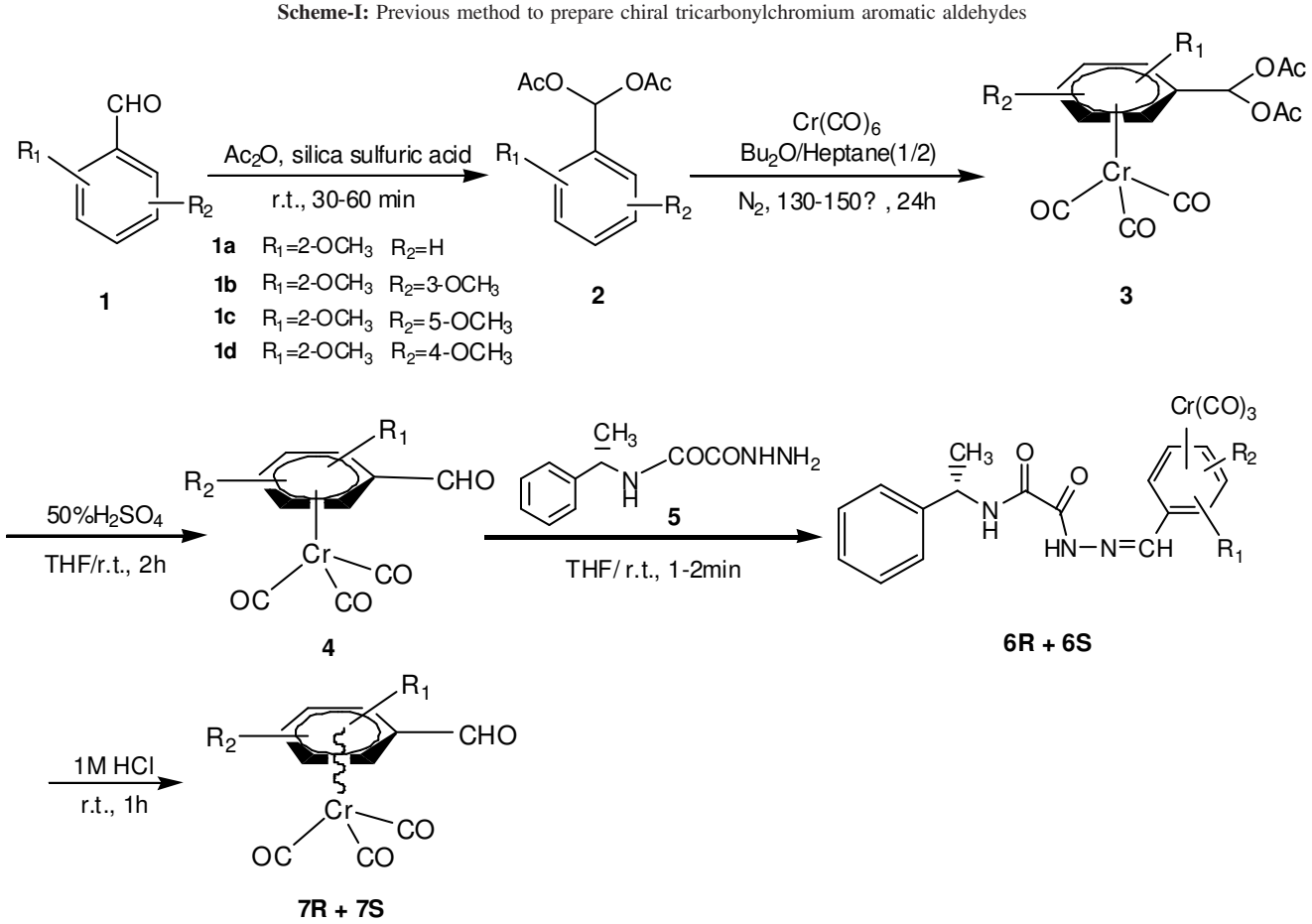
All reagents were purchased from commercial sources and used without further purification. TLC analysis was performed with glass backed plates precoated with silica gel and examined under UV (254 nm). NMR spectra were measured in $CDCl_3$ with Me_4Si as the internal standards on a Bruker Advance DPX-400 at room temperature. IR spectra were recorded on Bruker FTIR spectrometer, absorbance were reported in cm^{-1}. Mass spectra was determined by using a TOF-MS high resolution mass spectrometer. The ee % of compounds was determined by HPLC chromatograms.

Synthesis of chiral tricarbonylchromium(0) aromatic aldehydes: The reactions were monitored by TLC. The synthesis of **2** (**Scheme-II**, Table-1) based on our previous work[7] without solvent, the usage of sulfuric acid and THF in the achievement of **4** at room temperature in 1-2 min. All steps were according to **Scheme-II**.

In order to investigate this field, we must shorten the total time and increase the total yield. Based on the above rationale,



Scheme-I: Previous method to prepare chiral tricarbonylchromium aromatic aldehydes



Scheme-II: Improved method in this work

in this paper, we mainly introduced a simpler and more efficient synthesis of η^6-arene tricarbonylchromium(0) complexes than previous methods and used it as chiral auxiliary to induce aldol reaction to get chiral β-hydroxide ketone. The preparations of racemic tricarbonylchromium(0) aromatic aldehydes were shown in **Scheme-II** and Table-1.

Firstly, we made an improvement in the synthesis of **2** (**Scheme-II**, Table-1) based on our previous work[7] without solvent, which avoided using organic solvent (benzene) and give high yield. Secondly, the usage of sulfuric acid and THF to obtain **4** at room temperature gave 90 % yield in very short time (1-2 min). In the 4th step, the yield was very low due to tricarbonylchromium(0) aromatic aldehydes were unstable in acidic condition and removing of resoluting agent was difficult. Meanwhile, the tricarbonylchromium(0) group lost easily. These results mean a majority of efforts going to be waste. So, at last, a progress in the resolution of **4** was also developed in which the solvent was changed to THF (Table-2) which resulted in higher yield and remarkable shorter times at room temperature.

TABLE-1
SYNTHETIC RESULTS OF COMPOUNDS **2**, **3** AND **4**

Entry	R_1	R_2	Time (h)	Yield (%)
2a	2-OCH_3	H	2.5	90
2b	2-OCH_3	3-OCH_3	3.5	92
2c	2-OCH_3	5-OCH_3	3.5	89
2d	3-OCH_3	4-OCH_3	3.5	89
3a	2-OCH_3	H	18.0	72
3b	2-OCH_3	3-OCH_3	24.0	71
3c	2-OCH_3	5-OCH_3	24.0	73
3d	3-OCH_3	4-OCH_3	24.0	71
4a	2-OCH_3	H	0.15	88
4b	2-OCH_3	3-OCH_3	0.15	86
4c	2-OCH_3	5-OCH_3	0.15	89
4d	3-OCH_3	4-OCH_3	0.15	86

TABLE-2
EFFECT OF SOLVENT ON THE SYNTHESIS OF COMPOUND **6**

Entry	Solvent	Time (min)	T (ºC)	Yield (%)
1	THF	1	r.t.	94
2	DMF	10	r.t.	0
3	DMSO	10	r.t.	0
4	Cyclohexane	240	r.t.	0
5	Benzene	240	80	85

As we known, the aldol reaction between aromatic aldehydes and ketone is one of the most important reactions in forming C-C bond and the product named β-hydroxide ketone was an important skeletone unit in synthesizing natural products. The general ee % of asymmetric aldol reaction is ranging from 30-99 % mainly based on the reaction condition[8-13].

Spectra data of products

Compound +7a: $[\alpha]^{20}_D$ =1030º (c 0.10, $CHCl_3$) (lit.[1] + 1010º, c 0.06), e.e = 98.0 %, HPLC: *n*-hexane/2-propanol = 90:10, flow rate 1 mL/min, λ = 254 nm, t = 13.11 min, IR (KBr, ν_{max}, cm^{-1}): 3075, 3020, 2930, 2840, 2810, 1975, 1900, 1675, 1540, 1470, 990, 950, 890, 840, 805, 660. ^{1}H NMR (DMSO-d_6) (δ, ppm): 3.86 (3H, s, CH_3O), 5.40 (1H, t, *J* = 6.0 Hz, $Cr(CO)_3$-ArH), 5.79 (1H, d, *J* = 7.2 Hz, $Cr(CO)_3$-ArH), 6.35 (2H, d, *J* = 6.0 Hz, $Cr(CO)_3$-ArH), 9.98 (1H, s, CHO).

Compound 7a: $[\alpha]^{20}_D$ = -1020º (c 0.12, $CHCl_3$) (lit.[1] -1000º, c 0.09), e.e = 97.5 %, HPLC: *n*-hexane/2-propanol = 90:10, flow rate 1 mL/min, λ = 254 nm, t = 14.31 min, IR and ^{1}H NMR are identical with **+7a**.

Compound +7b: $[\alpha]^{20}_D$ = +370º (c 0.12, $CHCl_3$) (lit.[1] +360º, c 0.06), e.e = 98.0 %, HPLC: *n*-hexane/2-propanol = 90:10, flow rate 1 mL/min, λ = 254 nm, t = 13.79 min, IR (KBr, ν_{max}, cm^{-1}): 3075, 3015, 2930, 2860, 2820, 1970, 1900, 1670, 1540, 1475, 990, 956, 889, 840, 660. ^{1}H NMR (DMSO-d_6) (δ, ppm): 3.82 (3H, s, CH_3O), 3.93 (3H, s, CH_3O), 5.18 (1H, t, *J* = 6.0 Hz, $Cr(CO)_3$-ArH), 5.50 (1H, d, *J* = 6.0 Hz, $Cr(CO)_3$-ArH), 5.67 (1H, d, *J* = 6.0 Hz, $Cr(CO)_3$-ArH), 9.97 (1H, s, CHO).

Compound -7b: $[\alpha]^{20}_D$ = -380º (c 0.20, $CHCl_3$) (lit.[1] -387º, c 0.09), e.e. = 97.0 %, HPLC: *n*-hexane/2-propanol = 90:10, flow rate 1 mL/min, λ = 254 nm, t = 14.44 min, IR and ^{1}H NMR are identical with **+7b**.

Compound 9a: Colourless liquid, IR (liquid, ν_{max}, cm^{-1}): 3500, 3091, 3022, 2990, 2943, 2910, 2843, 1715, 1580, 1525, 1460, 1413, 1362, 1280, 1207, 1160, 1042, 997, 913, 886, 841, 798, 746, 675, 628. ^{1}H NMR (DMSO-d_6) (δ, ppm): 1.28 (1H, s, OH), 2.21 (3H, s, CH_3), 2.82-2.85 (1H, m, CH_2), 2.88-2.98 (1H, m, CH_2), 3.86 (3H, s, CH_3O), 5.43 (1H, dd, J_1 = 9.2 Hz, J_2 = 3.2 Hz, CH), 6.88 (1H, d, *J* = 8.0 Hz, ArH), 7.00 (1H, t, *J* = 6.8 Hz, ArH), 7.28 (1H, t, *J* = 6.8 Hz, ArH), 7.46 (1H, dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, ArH). HPLC: *n*-heptane/isopropanol = 95:5, flow rate 1 mL/min, λ = 254 nm, when using racemic aldehydes as substrates: **+9a**: e.e. = 37 %, **-9a**: e.e = 36 %.

Compound 9b: Colourless liquid, IR (liquid, ν_{max},cm^{-1}): 3505, 3089, 3020, 2990, 2941, 2905, 2840, 1720, 1578, 1526, 1458, 1411, 1361, 1282, 1205, 1162, 1041, 995, 910, 886, 840, 796, 747, 673, 632. ^{1}H NMR (DMSO-d_6) (δ, ppm): 1.25 (1H, s, OH), 2.22 (3H, s, CH_3), 2.83-2.86 (1H, m, CH_2), 2.85-2.99 (1H, m, CH_2), 3.88 (3H, s, CH_3O), 3.91 (3H, s, CH_3O), 5.43 (1H, dd, J_1 = 9.2 Hz, J_2 = 3.2 Hz, CH), 7.20 (1H, t, *J* = 8.0 Hz, ArH), 7.28 (1H, d, *J* = 8.0 Hz, ArH), 7.38 (1H, d, *J* = 8.0 Hz, ArH). HPLC: *n*-heptane/isopropanol = 95:5, flow rate 1 mL/min, λ = 254 nm, when using racemic aldehydes as substrates: **+9b**: e.e. = 28 %, **-9b**: e.e. = 26 %.

RESULTS AND DISCUSSION

In this paper, it was found that some complexes bearing tricarbonylchromium(0) group could react with acetone. Considered that the electron withdrawing of tricarbonylchromium(0) group played an important role in the reaction, we utilized it to get chiral β-hydroxide ketone by two steps: firstly, chiral tricarbonylchromium(0) aromatic aldehydes reacted with acetone catalyzed by chiral proline, secondly, tricarbonylchromium(0) group was removed by virtue of light (**Scheme-III** and Table-3). Considering the poor yields of chiral compound **7c (R+S)**, **7d (R+S)**, we only applied **7a**, **7b** in aldol reaction to get **9a**, **9b**. The results indicated that both L-proline and D-proline played the same catalyzing and stereoselective role in corresponding racemic compounds, respectively. The ee % of products were lower, it showed the necessary improvement

when chiral tricarbonylchromium(0) aromatic aldehydes were used as chiral reactant.

Conclusion

A simpler and more efficient synthesis method of η^6-arene tricarbonylchromium(0) complexes is developed and used them as chiral auxiliary to induce aldol reaction to get chiral β-hydroxide ketone. Some improvements were achieved: shorter total times (from 60-32 h) were taken with higher total yields (from 23-57 %) at room temperature comparing with previous methods. Their asymmetric aldol reactions is also investigated with acetone in detail at room temperature. The ee % of products were lower, it showed the necessary improvement when chiral tricarbonylchromium(0) aromatic aldehydes were used as chiral reactant.

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