Communication

Studies on Tripolycyanamide Formaldehyde Resin-Pd Complex and Its Use in the Synthesis of the Branch of Paclitaxel

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A novel method was developed to prepare the branch of paclitaxel using 2,4-dichlorophenylaldehyde as the starting material. The branch was synthesized through condensation, cycloaddition and catalyzing hydrogenation of dichlorophenyl intermediate. Tripolycyanamide formaldehyde resin-Pd complex as hydrogenation catalyst has been studied. The influence of temperature and N/Pd atomic ratio of the catalyst on the effect of catalytic hydrogenation was investigated and the optimum conditions were found. Because of the mild cyclization reaction condition, convenient asymmetric resolution operation and high yield, the synthetic route was practical.

Keywords paclitaxel, catalytic hydrogenation, polymer-Pd catalyst

Taxol (paclitaxel) is currently thought to be one of anticancer pharmaceuticals with the most remarkable curative effects[1-3] on mammary gland cancer, lung cancer, stomach cancer and crown cancer.[4,5] Due to its complex structure with many functional groups and chiral centers, the total synthesis of paclitaxel has become a challenge. As 10-deacetylbaccatin III (10-DABIII) could be extracted in large quantity from European *Taxus baccata*,[6,7] effective partial synthesis is going to decrease the cost of paclitaxel dramatically.

Since 1980's, the field of polymeric metal catalysts, which were obtained by fixing the catalytic active metal to polymer carriers, has been a focus of scientists' interest.[8-11] This kind of catalysts have both the merits of homogeneous characteristics (such as high activity, good selectivity and mild reaction condition), and heterocatalysts (easy separation from products and not corroding apparatus). Study of catalytic hydrogenation of chloroarene to arene with this kind of catalysts has not been reported previously. We have studied the preparation and characteristics of tripolycyanamide formaldehyde resin-palladium. When the catalyst was heated to above 200 ℃, the degree of polymerization of tripolycyanamide formaldehyde resin (TCR) was increased, at the same time the loading capacity of TCR to Pd or Pd^{2+} was obviously enhanced. In the experiment, it was occasionally found that tripolycyanamide formaldehyde resin-Pd (TCR-Pd) can catalyze the reaction of chlorophenyl aldehyde to toluene when the N/Pd atomic ratio of the catalyst decreased to specific extent. So TCR-Pd catalyst was applied to the synthesis of the branch of paclitaxel, (2*R*, 3*S*)-(−)-benzoyl-3-phenyl-isoseriine methyl ester.

[(3*R*,4*S*)-3-hydroxy-*N*-[(*S*)-(1-phenyl) ethyl]-4-(2′,4′-dichlorophenyl)-azetidin-2-one] (**4**) can be obtained in high yield, hence it would be an effective and cheap way to synthesize paclitaxel if chlorobenzene could be reduced to benzene. So we adopted tripolycyanamide formaldehyde resin-Pd (TCR-Pd) complex as catalyst to catalyze hydrogenation of dichlorophenyl compound and obtained the side chain of paclitaxel (Scheme 1).

Results and discussion

Characteristics of the catalyst

According to the colors of the catalysts before and after activation (red before activation and black after activation), it can be concluded in preliminary that the oxidation state of the palladium was 2+ (Pd^{2+}) in the fresh catalyst or 0 (Pd^0) in the activated catalyst.

In order to check and verify the valence state further, EPR (electron paramagnetic resonance) spectra of the catalyst were recorded before and after activation. When Pd^{2+} in catalyst was reduced to Pd^+ and Pd^0, the numbers of single d electrons decreased from 1 to 0. A single electron peak ($H\gamma$ = 3.367 gaus) was observed for TCR; while the fresh TCR-Pd owned two single electron peaks ($H\gamma$ = 3.367 gaus and $H\gamma$ = 2.967 gaus), the g values of which were 2 and 2.268 [$g = h\nu/\beta H\gamma$ ($\beta = 9.278 \times 10^{-2}$ erg/gaus)]. The peak (g = 2) was free radical peak (perhaps from polymeric supporter), while the peak ($g > 2$) was single electron peak with more than 5 d electrons.[12] So the peak at $H\gamma$ = 2.967 gaus (g = 2.268) may be $3d^8$ single electron peak of Pd^{2+} or $3d^9$ single electron peak of Pd^+ (Pd^{2+} may be reduced to Pd^+ by a few formaldehyde

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Scheme 1 Synthetic route of paclitaxel

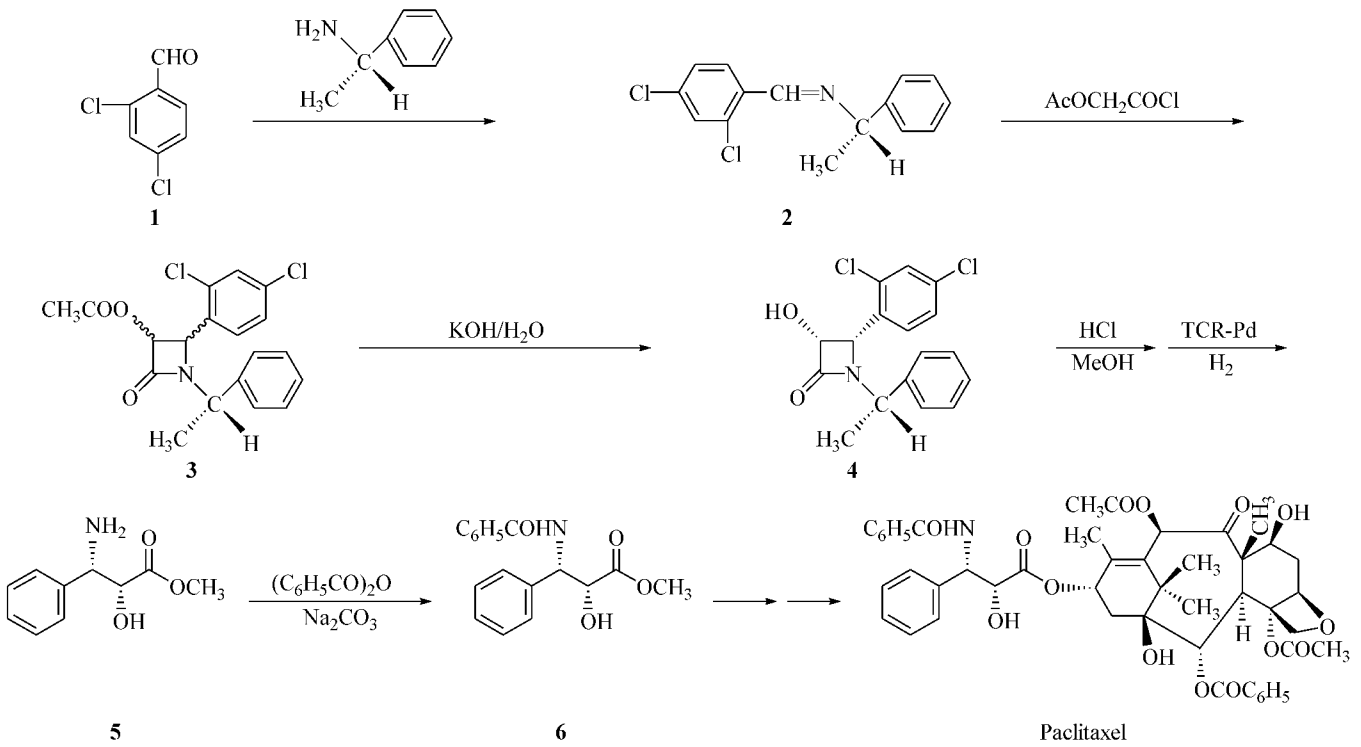

Table 1 XPS data of palladium in the catalyst (eV)

Atomic orbit	Fresh catalyst	Reduced catalyst	$PdCl_2$	$PdCl_2$[14]	Pd black[14]
$Pd_{3d5/2}$	337.1	335.5	338.1	338.0	335.2
$Pd_{3d3/2}$	342.4	340.7	343.5	343.3	340.2

in TCR). The facts that the single electron peak at $H\gamma$ = 2.967 gaus (g = 2.268) for activated catalyst disappeared and the free radical peak of the polymer still existed, proved that d-orbit of the activated catalyst was completely filled and the palladium in catalyst was Pd^0.

For confirming valence state change of Pd in the catalyst, we measured X-ray photoelectron spectroscopy (XPS) of $PdCl_2$, catalysts before and after activation. From Table 1, the binding energies of $3d_{5/2}$ and $3d_{3/2}$ for Pd in activated catalyst were decreased 1.6 eV and 1.7 eV respectively. Referring to the value of the electron binding energy of Pd black and $PdCl_2$ in literature and the amount of absorbing hydrogen in pre-activated procedure,[13] the palladium in catalyst was further proved to be Pd^{2+} before activation and Pd^0 after activation.

In addition, to judge whether palladium in activated catalyst had formed crystal, we determined X-ray diffraction (XRD) for the supporter and catalyst. The spectra of XRD showed that TCR and TCR-Pd owned a smooth peak (belonging to non-crystalline peak), while for activated catalyst, besides original non-crystalline peak there existed three small dispersion peaks at the diffraction position of Pd crystal, the Bragg angles of which were 40°, 44° and 64° respectively. According to $2d\sin\theta = \lambda$, the values of d can be calculated to be 2.25, 2.05 and 1.45 close to the values of Pd (2.25, 1.95 and 1.38). So it proved that small crystal grains were formed via accumulation of Pd at the local surface of the activated catalyst.

In short, TCR was complexed with Pd^{2+} in the fresh catalyst and the valence of Pd in activated catalyst was 0. Because active centers of unsaturated metastable state caused by coordination were fixed or stabilized by polymer ligands, or combined with the supporter in the form of low accumulated clusters, the coordinate bond among ligating atoms were relatively weakened in the course of catalyzing, leading to easy exchanging of ligands. It may be one of the causes for the high activity of this kind of catalyst.

Hydrogenating activity of the catalyst is affected in many aspects. Different degree of polymerization will change the surroundings, the steric hindrance, and the cooperative effect of Pd. When the molar ratios of $C_3H_6N_6$ to formaldehyde are 1∶1 and 1∶2, the obtained TCR has difficulty to complex with Pd; When the ratio is 1∶6 and the polymerizing temperature is 220 ℃, the TCR has strong complexing ability with Pd and can react with Pd rapidly in ethanol solvent at the room temperature.

The N/Pd atomic ratio in TCR-Pd plays a key role to decide whether the TCR-Pd can catalyze hydrogenated chlorine atom. When TCR-Pd contains 3% Pd (the N/Pd atomic ratio is around 9.6), it can only catalyze hydrogenated benzyl groups and not catalyze hydrogenated chlorine atoms to hydrogen atoms at 50 ℃. Under the same condition, TCR-Pd containing 10% Pd (the N/Pd atomic ratio is around 20.5) can reduce not only benzyl groups but also chlorine atoms at the same time and make the reaction end in 3 h. So TCR-Pd, containing 8%—20% Pd (the N/Pd atomic ratio is around 25.6—12.8), owns good catalytic hydrogenation ability to chlorine atom. By exploring influences of temperature and solvent, the optimal temperature of catalytic hydrogenation is 35—45 ℃, and alcohol solvents, especially methanol and ethanol, have good catalytic effects.

Synthesis

Acetoxyacetyl chloride, which was used to prepare 2-lactam[14] was very sensitive to water. The dropping of the solution of acetoxyacetyl chloride in chloroform was a long procedure and trace water in chloroform would react with the chloride to afford the corresponding carboxylic acid, which was undissolvable in chloroform and could not react with Schiff base resulting in difficulty of dropping and dramatic decrease of the yield. So chloroform must be adequately dried with anhydrous $CaCl_2$ in order to eliminate the influence of the water. According to the literature,[14] the system temperature during dropping of acetoxyacetyl chloride should be controlled at −20 ℃ and then raised to above 0 ℃, and the reaction ended after stirring for many hours. However, when we employed chlorobenzaldehyde instead of benzaldehyde in cyclization, −5—10 ℃ was appropriate temperature and the reacting time was shortened evidently.

The intermediate lactam (**3**) was so viscous that its isomers can not be resoluted by recrystallization. Hydrolysis and recrystallization with the mixed solvent of ethyl acetate and *n*-hexane (volume ratio : 9/1) afforded [(3*R*, 4*S*)-3-hydroxy-*N*-[(*S*)-(1-phenyl) ethyl]-4-(2′,4′-dichlorophenyl)-azetidin-2-one] (**4**) in high yield (the total yield of the preceding three steps was about 61.9%).

Finally by benzoyl reaction, the branch of paclitaxel (**6**) was obtained in high yield.

In conclusion, TCR-Pd containing 10% Pd can catalyze the hydrogenation of dichlorophenyl to phenyl in methanol in nearly 100% yield at 35—45 ℃.

Experimental

Apparatus

Melting points were determined on an RY-1 melting point apparatus and were not corrected. Infrared spectra were recorded on a Hitachi 260-50 spectrophotometer. ^{1}H NMR spectra were measured on a Brucker-500 MHz spectrometer using TMS as an internal standard. Optical activity was performed using a Perkin-Elmer 241 MC polarimeter. The TCR was synthesized with the literature method.[15] The measurement of contents of Pd and N of catalyst is as follows: the content of Pd was measured using the way of weighing after the catalyst was burned completely at high temperature, the content of N was tested using Kjeldahl way.

Preparation of the catalyst TCR-Pd

To a 50-mL flask was added TCR, $PdCl_2$ and 20 mL anhydrous alcohol. The reaction finished after stirring for 2 h at room temperature.

Synthesis of [(3*R*,4*S*)-3-*hydroxy*-*N*-[(*S*)-(1-*phenyl*)*ethyl*]-4-(2′,4′-*dichlorophenyl*)-*azetidin*-2-*one*] (**4**)

To a 100-mL flask was added 0.011 mol 2,4-dichlorophenylaldehyde, 15 mL trichloromethane, 0.010 mmol (*S*)-1-phenylethylamine and 40 nm molecular sieves. The mixture was stirred for 12 h, and then filtered. After removal of the solvent, a white viscous solid (Schiff base of 2,4- dichlorophenylaldehyde) was obtained.

The schiff base was dissolved in 20 mL of trichloromethane and triethylamine (0.021 mol, 2.9 mL) and the mixture was cooled to −5—0 ℃ in an ice-salt bath. The solution of acetoxyacetyl chloride (0.012 mol, 1.6 mL) and trichloromethane (15 mL) was added dropwise. The reaction mixture was continued to stir for 2—4 h at room temperature and acidified by 20 mL of 2.7 mol·L^{-1} HCl solution. The resulting solution was washed twice with water (20 mL) and the organic layer was collected and dried over $MgSO_4$. After removal of the solvent, a brown viscous liquid, 3-acetoxy-4-(2,4-dichlorophenyl)-2-(1-phenylethyl)-azetidin-2-one (**3**), was obtained.

To a mixture of 3 mol·L^{-1} KOH solution (13 mL) and THF (15 mL) was added dropwise the solution of **3** in THF (9 mL) at 0—3 ℃. After 2.5 h, the resulting solution was adjusted to pH = 9 with 30 mL of saturated $NaHCO_3$ solution, and the organic layer was extracted three times respectively using 20, 20 and 15 mL ethyl acetate, then dried over $MgSO_4$. After removal of solvent, a yellow solid was obtained. Chiral 3-hydroxy azetidin-2-one (**4**) was resoluted by recrystallization. White crystal (2.08 g) was obtained in 61.9% total yields of the preceding three steps by recrystallization in the mixture solvents of ethyl acetate and *n*-hexane (volume ratio : 9/1). m.p. 154—157 ℃, $[\alpha]_D^{20}$ + 212 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.26—7.42 (m, 8H, Ar), 5.10 (d, *J* = 4.7 Hz, 1H, C**H**OH), 5.03 (d, *J* = 4.7 Hz, 1H, CHN), 4.94 (q, *J* = 7.2 Hz, 1H, C**H**CH_3), 1.50 (d, *J* = 7.2 Hz, 3H, CHC**H**$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 169.9, 140.0, 135.0, 134.8, 131.9, 131.2, 129.9, 129.3, 128.6, 127.5, 127.3, 77.1, 59.2, 53.7, 19.9; IR (KBr) ν: 3258, 2990, 2900, 1718

cm^{-1}; MS *m/z* (%): 337.0 ($M + H^+$, 7.8). Anal. calcd for $C_{17}H_{15}NO_2Cl_2$: C 60.73, H 4.50, N 4.17; found: C 60.96, H 4.41, N 3.94.

Synthesis of (2*R*,3*S*)-*beta-phenyl isoserine methyl ester* (**5**)

The mixture of **4** (12 mmol) and 45 mL saturated methanol solution of HCl was stirred for 3—8 h and the solvent was removed, the resulting solid was dissolved in distilled water and neutralized by 7.5 $mol \cdot L^{-1}$ NaOH in the ice-water bath. The organic layer was obtained by extracting with CH_2Cl_2 (35 mL × 3). After removal of solvent, a yellow product was obtained in nearly 90% yield.

The catalyst was swollen in 20 mL methanol and 8 mL glacial acetic acid and pre-activated under hydrogen atmosphere for 4 h, followed by adding ring-opening chloro compound obtained above. After stirring for 5—8 h at room temperature and in the hydrogen atmosphere, the catalyst and solvent were removed, and distilled water and CH_2Cl_2 were added. The resulting mixture was neutralized with 3 $mol \cdot L^{-1}$ NaOH under stirring in the ice-water bath. The solvent was removed from the obtained organic layer to afford light yellow solid. Recrystallization with ethyl acetate/isopropyl ether (volume ratio: 2/1) gave the white crystal (**5**) in 60.8% yield. m.p. 103—106 ℃ (Lit.[16] 106—108 ℃), $[\alpha]_D^{20}$ − 22 (*c* 1.0, MeOH); ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.20—7.42 (m, 5H, Ar), 4.35 (d, *J* = 9 Hz, 1H, C**H**N/C**H**OH), 4.33 (d, *J* = 9 Hz, 1H, C**H**N/C**H**OH), 3.80 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 174.2, 142.2, 129.0, 128.1, 127.1, 75.3, 58.2, 53.1; IR (KBr) ν: 3345, 3294, 3065, 2912, 1743, 1605, 1215, 1171, 1090 cm^{-1}; MS *m/z* (%): 195 (M^+, 12.5). Anal. calcd for $C_{10}H_{13}NO_3$: C 61.51, H 6.72, N 7.18; found: C 61.63, H 6.59, N 6.95.

Synthesis of (2*R*,3*S*)-(−)-*benzoyl-3-phenyl-isoseriine methyl ester* (**6**)

After 1.3 mmol **5** was dissolved in 25 mL dichloromethane in a 50-mL flask, the mixture of 1.4 mmol benzoic anhydride, 2 mmol Na_2CO_3 and 5 mL H_2O were added. The mixture was stirred for 6 h at room temperature. The solution was washed twice with water and the organic layer was separated and dried over $MgSO_4$. After removal of the solvent, white solid was obtained. Recrystallization with ethyl acetate/hexane (volume ratio: 3/2) gave the white crystal (**6**) in 90.2% yield. m.p. 183—185 ℃ (Lit.[17] 182—184℃), $[\alpha]_D^{20}$ − 48.5 (*c* 1.0, MeOH) (Lit.[17] $[\alpha]_D^{20}$ − 47.6, *c* 0.93, MeOH); ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.51—7.22 (m, 10H, Ar), 5.46 (d, *J* = 9 Hz, 1H, C**H**N/C**H**OH), 5.31 (d, *J* = 9 Hz, 1H, C**H**N/C**H**OH), 4.58 (s, 1H, NH), 3.92 (s, 3H, OCH_3), 3.23 (br, 1H, OH); IR (KBr) ν: 3501, 3298, 2971, 1739, 1683 cm^{-1}; MS *m/z* (%): 299 (M^+, 6.9). Anal. calcd for $C_{17}H_{17}NO_4$: C 68.23, H 5.69, N 4.68; found: C 68.02, H 5.88, N 4.92.

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