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Synthesis of 1,5-Bis(triphenylphosphonium)pentan-3-ol Dichloride and Its Application to the Preparation of 1,7-Di(pyridin-3-yl)heptan-4-ol

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Abstract:

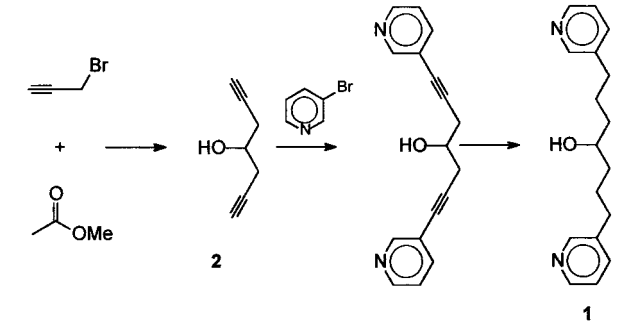
The preparation of *1,7-di(pyridin-3-yl)-heptan-4-ol* (1), an important intermediate in the synthesis of a series of novel cancer multidrug resistance (CMR) chemosensitizers, has been accomplished in high overall yield via the new bis-Wittig reagent *1,5-bis(triphenylphosphonium)pentan-3-ol dichloride* (6), that can also be used in the preparation of other members of the class of CMRs.

1,7-Diaryl- and 1,7-diheteroaryl-heptan-4-ols are important intermediates in the synthesis of a series of novel cancer multidrug resistance (CMR) chemosensitizers, recently developed and patented by Vertex Pharmaceutical Inc.[1] Among them, the heterocyclic compound 1,7-di(pyridin-3-yl)-heptan-4-ol (**1**) is the most interesting derivative. The reported preparation of **1** is represented in Scheme 1 and entails Pd-catalysed double-Heck coupling of 3-bromopyridine to hepta-1,6-diyne-4-ol (**2**), followed by hydrogenation.[1] However, the difficult and low-yielding synthesis of the required intermediate **2** makes this route unsuitable for an industrial scale-up as well as quite expensive.

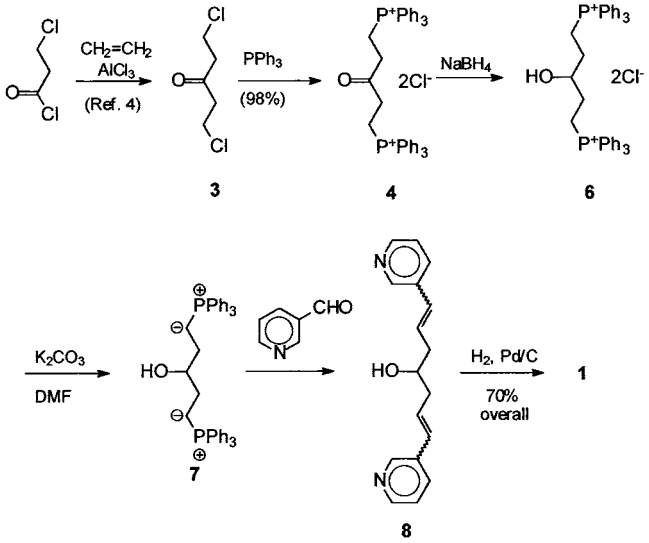
Other synthetic approaches, such as the double addition of a lithio(hetero)aryl acetylene on epibromohydrin followed by hydrogenation,[2] also require expensive reagents and are not adaptable to large-scale industrial applications. The obvious approach of a Grignard addition of 3-(3′-pyridyl)-propylmagnesium chloride to a formate ester is also not feasible both because of the known high reactivity of the Grignard reagent to intramolecularly cyclise to 2,3-pyrindane[3] and because of the high cost of 3-pyridinepropanol, the starting material for the preparation of the above Grignard reagent. Here we present a rapid and high-yielding procedure for the preparation of **1**, adaptable to multikilogram scale, that makes use of the bis-Wittig reagent **6** as the key intermediate. The latter compound **6** can be double-deprotonated with a base to form the corresponding bis-ylide **7** which reacts with nicotinaldehyde to afford product **8** which upon hydrogenation generates the title compound **1** (Scheme 2). The present method employs for the Wittig reaction a procedure that avoids the use of strong bases and strictly anhydrous conditions and has been successfully scaled up to 50-kg scale in our pilot plant.

Reaction of 1,5-dichloropentan-3-one **3** (readily available by Friedel−Craft acylation of ethylene with 3-chloropropionyl chloride[4]) with triphenylphosphine affords the bisphosphonium salt **4**. Although the reaction can be carried out in a great variety of solvents (toluene, acetonitrile, acetone, 2-butanone), the best results are obtained by heating the two reagents in DMF at 80−100 °C. On a large-scale preparation, the reaction can be conveniently performed by adding the dichloroketone to a preheated concentrated solution of triphenylphosphine in a DMF/toluene mixture. The bisphosphonium salt precipitates during the addition of the dichloroketone and can be isolated by filtration after cooling. Because of the substantial loss of material during isolation of the poorly stable dichloroketone **3**, the reaction is best carried out in a one-pot procedure directly from 3-chloropropionyl chloride and delivers 1,5-bis(triphenylphos-

Scheme 1



Scheme 2



(1) Zelle, R. E.; Harding, M. W. PTC Int. Appl. WO 95/26337, October 4, 1995.
(2) Wang, Z.; Deschenes, D. *J. Am. Chem. Soc.* **1992**, *114*, 1090−1091.
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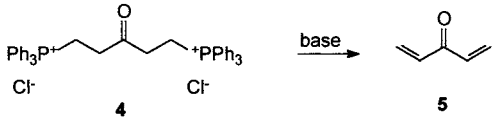
Scheme 3



phonium)-pentan-3-one dichloride **4** as a colourless crystalline solid in high yields (92−98.5% from 3-chloropropionyl chloride) and high purity (>95% by TLC and NMR). This salt is a nonhygroscopic, thermally stable solid in the pure state, but it decomposes readily under basic conditions, either in water (NaOH, Na_2CO_3 solutions) or in organic solvents (MeONa in MeOH, BuLi in THF) with elimination of triphenylphosphine and formation of the highly reactive divinyl ketone **5** (Scheme 3; due to the its relatively high stability, this diphosphonium salt **4** might be considered for other applications. It is an alternative to 1,5-dichloropentanone **3**, a precursor of the widely used divinyl ketone and related reagents.[5]) Due to its instability under basic conditions, the intermediate 1,5-bis(triphenylphosphonium)pentan-3-one dichloride **4** is unsuitable for Wittig and related reactions, which employ basic conditions to generate the corresponding ylide. To overcome this problem, ketone **4** is thus reduced to the corresponding alcohol **6** with sodium borohydride (0.30 mol equiv) in water. The reduction is fast and quantitative even at 5−10 °C; the only minor impurity is triphenylphosphine (1−3%), generated from a slight decomposition of the bisphosphonium salt in the fairly basic sodium borohydride medium. The product bisphosphonium pentanol dichloride **6** can be isolated from the reaction mixture in almost quantitative yield after acidification to pH 2−3 with concentrated HCl, filtration of triphenylphosphine impurities, concentration and extraction with dichloromethane. The product, which crystallises on standing, is a hygroscopic colourless solid indefinitely stable if kept under exclusion of moisture.

Generally, deprotonation to form bis-ylides similar to **7** is accomplished with strong bases (e.g., *t*-BuOK, *n*-BuLi, LiHMDS, NaH, etc.).[6] All attempts of double deprotonation of **6** with 2 equiv or more of these bases either in the absence or presence of 3-pyridinecarboxaldehyde (nicotinaldehyde) are fully unsuccessful, leading to extensive decomposition of the bisphosphonium salt and formation of triphenylphosphine. By variance of standard Wittig conditions fairly good results are obtained using the two-phase, solid−liquid technique devised by Delmas et al.[7] employing anhydrous potassium carbonate in refluxing 2-propanol. Under these reaction conditions, in the presence of stoichiometric amounts of nicotinaldehyde, a mixture of all possible isomers (*E*,*E* + *E*,*Z* + *Z*,*Z*) of **8** is obtained in fair yield and low conversion. The reaction cannot be taken to completion even

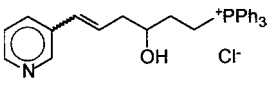


Figure 1.

with an excess of potassium carbonate and after a long refluxing time. Furthermore, some decomposition occurs when heating is protracted to long reaction times. These drawbacks are avoided by carrying out the reaction in DMF at 120−130° C for 5−7 h or, even better, in a toluene/DMF mixture at reflux for 5−7 h, azeotropically distilling the water produced by the reaction. Under these conditions, over 95% conversion can be achieved with little or no decomposition. The HPLC analysis of the crude reaction mixture reveals the presence of trace amounts of unreacted nicotinaldehyde and monoreacted intermediate **9** (Figure 1).

Workup entails addition of water to the reaction mixture to dissolve the inorganic salts and most of DMF, separation of the organic phase, and extraction of the aqueous one with ethyl acetate or a toluene/ethyl acetate mixture. The combined organic phases are extracted with 10% sulfuric acid. The organic layer containing triphenylphosphine oxide is discharged, while the aqueous phase containing the product is directly submitted to catalytic hydrogenation of the double bonds using 5% Pd/C as catalyst and hydrogen pressure of up to 5 bar. After filtration of the catalyst, the pH of the solution is adjusted to ca. 10 with 30% NaOH solution, and the crude final product **1** is extracted with ethyl acetate or a toluene/ethyl acetate mixture. Purification is achieved by crystallization of the monosuccinate salt of **1** from a polar solvent; the best results are obtained using acetone. 1,7-Di-(pyridin-3-yl)heptan-4-ol monosuccinate **10** is isolated as an off-white crystalline solid with a purity higher than 99.0% (HPLC, area %). The yield of **10** from 1,5-bis(triphenylphosphonium)pentan-3-one dichloride **4** is ca. 70%, and the overall yield of the entire reaction sequence starting from 3-chloropropionyl chloride (Scheme 1) is typically 65%.

The present procedure can be properly adapted to the synthesis of other symmetrically substituted 1,7-diaryl or diheteroaryl heptan-4-ol derivatives. The isolation of these derivatives can be carried out by normal purification methods involving either crystallization or chromatographic separation procedures.

Experimental Section

Proton NMR spectra were recorded on a Varian Gemini 2000 operating at 300 MHz. Mass spectra were recorded on a HP 5972 mass selective detector coupled with a HP 6890 GC system.

HPLC chromatograms were recorded on a HPLC system HP series 1100 using a Nucleosil C18 AB column, length 250 mm, i.d. 4.6 mm. Eluent A: tetrabutylammonium hydrogensulfate 10 mM buffer at pH 8/methanol 80:20. Eluent B: tetrabutylammonium hydrogensulfate 10 mM buffer at pH 8/methanol 20:80. Mobile phase: 100% eluent A for 5 min, linear gradient to 100% eluent B over 30 min. Flow rate 1.0 mL/min. UV detector, wavelengh 254 nm.

1,5-Dichloropentanone (3). In a 1000-L glass-lined reactor a suspension of anhydrous aluminium trichloride

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(42.8 kg, 321 mol) in dichloromethane (201 L) is cooled to 0° C under a nitrogen atmosphere, and 3-chloropropionyl chloride (40.0 kg, 315 mol) is added under stirring over ca. 30−60 min. Ethylene gas (ca. 13.0 kg, 464 mol) is bubbled into the cloudy suspension for a period of 2−3 h while keeping the temperature below 5° C. The resulting clear mixture is slowly poured into a second 2000-L glass-lined reactor containing toluene (217 L), concentrated HCl (22 L) and water (130 L), keeping the temperature below 10° C. The resulting biphasic mixture is stirred for ca. 30 min, the lower aqueous layer is discharged, the organic layer is concentrated under vacuum at ca. 20−40° C to obtain a toluenic solution of 1,5-dichloropentanone with 90−95% purity (by GLC) which is used directly in the next step.

1,5-Bis(triphenylphosphonium)pentan-3-one Dichloride (4). In a 1000-L glass-lined reactor triphenylphosphine (165.5 kg, 631 mol), DMF (87 L) and toluene (130 L) are consecutively charged and the resulting solution is heated to 90° C under a nitrogen atmosphere. The above solution of crude 1,5-dichloropentan-3-one is added over about 2−3 h at 90−100° C. The resulting suspension is stirred at 100−105° C for 3−5 h, cooled to 20−25° C, and stirred for an additional hour. The precipitate is filtered through a filter-drier, washed with acetone (130 L), and vacuum-dried at 40−50° C until constant weight, obtaining the bisphosphonium salt **4** as a colorless crystalline solid (211.0 kg 98.5% yield over two steps): mp 214−217° C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 3.35 (complex m, 4H, H2, and H4), 3.92 (complex m, 4H, H1, and H5), 7.65−7.85 (complex m, 30H, aromatic protons).

1,5-Bis(triphenylphosphonium)pentan-3-ol Dichloride (6). In a 500-L stainless steel reactor sodium borohydride (1.7 kg, 44.94 mol, 0.305 equiv) is dissolved in demineralized water (50 L), and the resulting solution is cooled to 0° C. In a second 500-L stainless steel reactor 1,5-bis(triphenylphosphonium)pentan-3-one dichloride **4** (100.0 kg, 147.14 mol) is dissolved in water (200 L) at 20−30° C. This solution is added to the sodium borohydride solution over a period of 1 h while keeping the temperature below 10° C. The resulting white suspension is stirred at 15° C for another hour and then transferred into an 800-L glass-lined reactor. Concentrated HCl (10 L) is carefully added until reaching pH 2−3, and the reaction mixture is stirred for additional 30 min at 20−25° C. The byproduct triphenylphosphine is filtered off through a Sparkler filter which is washed with water (50 L). The clear filtrate is collected into an 800-L glass-lined reactor and concentrated under vacuum at 50−60° C/20 mbar to provide a slightly yellow oil which is dried by stripping with a 1:1 toluene/DMF mixture (2 × 100 mL) and used as such in the next step.

On a lab scale the crude oil can also be extracted with dichloromethane (3 × 150 mL per 100 g of 1,5-bis(triphenylphosphonium)pentan-3-one dichloride **4**). The organic solution is concentrated under vacuum, yielding about 100−105 g of crude product as a colourless oil which crystallizes on standing or by trituration with ethyl acetate (100 mL). The resulting solid is highly hygroscopic, preventing routine analysis. HPLC purity (area %): 98.5%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.80−2.10 (complex m, 4H, H2, and H4), 3,6 (complex q, 2H, H1, and H5), 3.85 (complex q, 2H, H1 and H5), 4.19 (broad t, 1H, H3), 7.65−7.85 (complex m, 30H, aromatic protons).

1,7-Dipyridin-3-yl-hepta-1,6-dien-4-ol (8). In an 800-L stainless steel reactor crude 1,5-bis(triphenylphosphonium)-pentan-3-ol (**6**) (100−105 kg, ca. 147 mol) is dissolved in DMF (100 L) and toluene (80 L). To the resulting solution are added pyridine-3-carboxaldehyde (32.0 kg, 298.75 mol, 2.03 equiv) and anhydrous K_2CO_3 (50.0 kg, 361.77 mol, 2.46 equiv). The heterogeneous mixture is heated to reflux (116°−128° C) for 6−8 h, azeotropically distilling the water formed and monitoring the reaction by HPLC until reaching a conversion higher than 96%. The resulting orange suspension is cooled to 20−25° C, transferred into a 1000-L glass-lined reactor, and water (550 L) is added. The biphasic mixture is strirred at 20−25° C for 30 min until complete dissolution of the inorganic salts is observed. The organic phase is separated and the aqueous layer extracted with toluene (100 L) and ethyl acetate (100 L). To the collected organic phases a solution of H_2SO_4 (96%, 10 L) and water (170 L) is added and the resulting biphasic mixture stirred for 30 min. The organic phase containing the byproduct triphenylphosphine oxide is discharged, and the acidic aqueous solution (approximately 240 L) with a product purity of 90% (by HPLC) is used as such in the next step.

1,7-Di(pyridin-3-yl)-heptan-4-ol Monosuccinate (10). The above solution is introduced into a 1000-L stainless steel autoclave, and moist 5% Pd/C (5.0 kg, 50% H_2O) suspended in water (20 L) is added. The vessel is purged with nitrogen and pressurized with hydrogen gas to 4 bar. The hydrogenation is carried out at 20−25° C for about 4−6 h or until hydrogen consumption ceases. The autoclave is purged with nitrogen, the catalyst is filtered off, and the filter cake is washed with water (100 L). The yellow solution is transferred into a 1000-L stainless steel reactor, and ethyl acetate (100 L) and toluene (100 L) are added. To the biphasic mixture 30% NaOH (80 L) is added until the pH reaches 10 or above. The organic phase is separated, and the aqueous layer is extracted with ethyl acetate (4 × 100 L). The collected organic phases are washed with water (100 mL) and concentrated under vacuum at 40° C/20 mbar, obtaining the crude **1** as an orange viscous oil, having a purity of 88−90% with 6−8% of 3-hydroxymethylpyridine (by HPLC). The crude oil is dissolved in acetone (70 L), and the orange solution is treated at 20−25° C with activated charcoal (1.5 kg). The suspension is filtered through a Sparkler filter with Dicalite plates, and the filter is washed with acetone (30 L). To the yellow solution, succinic acid (15.0 kg, 127.0 mol, 0.86 equiv) is added, and the mixture is heated to reflux for 30 min. The resulting solution is cooled to 0° C over a period of 1 h, and the suspension is stirred at 0−5° C for another hour. The precipitate is centrifuged, washed with acetone (25 L), and dried in a vacuum tray-drier at 40−50° C for ca. 8 h to deliver 1,7-di(pyridin-3-yl)-heptan-4-ol monosuccinate (**10**) as an off-white crystalline solid (40.5 kg, 104.2 mol, 70.8% overall yield from 1,5-bis(triphenylphosphonium)pentan-3-one dichloride **4**), 99.2% pure by HPLC. Mp

114.5−116° C (acetone), assay (NaOH titr.) 99.5%, LOD 0.15%.

^{1}H NMR (CD_3OD, 300 MHz) δ 1.40−1.52 (complex m, 4H, H_3, and H_5), 1.58−1.85 (complex m, 4H, H_2, and H_6), 2.55 (s, 4H, succinate), 2.7 (complex m, 4H, H_1, and H_7), 3.58 (complex m, 1H, H_4), 4.95 (s, 2H, pyridinium H), 7.37 (ddd, 2H, $H_{5'}$, $J_{4,5} = 7.8$, $J_{5,6} = 4.9$, $J_{2,5} = 0.7$), 7.72 (ddd, 2H, $H_{4'}$, $J_{2,4} = 3.2$, $J_{4,6} = 1.5$), 8.35 (dd, 2H, $H_{6'}$), 8.38 (dd, 2H, $H_{2'}$).

^{13}C NMR (CD_3OD, TMS) δ 28.3 ($C_{2,6}$), 30.0 (C_{succin}), 33.6 ($C_{1,7}$), 37.7 ($C_{3,5}$), 71.7 (C_4), 125.2 ($C_{5'}$), 138.5 ($C_{4'}$), 140.3 ($C_{3'}$), 147.4 ($C_{6'}$), 150.0 ($C_{2'}$), 176.4 (CO_{succin}).

MS (EI+, as free base): 270 (M^+, 6), 269 ($M^+ - H$, 25), 253 (M − OH, 6), 178 (M − $PyCH_2$, 60), 164 (18), 150 (35), 148 (22), 106 (62), 105 (58), 93 (100), 92 (38), 65 (24).

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