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PALLADIUM-CATALYZED SYNTHESIS OF SUBSTITUTED CYCLOPENTADIENES AND INDENES FROM ALLYLIC ESTERS

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Summary

Various mono- and di-substituted cyclopentadienes have been prepared by palladium-catalyzed alkylation of allylic esters with cyclopentadienide and t-butylcyclopentadienide anions. The same procedure has been applied to the preparation of substituted indenes.

Introduction

The cyclopentadienyl (Cp) ligand is widely encountered in transition-metal complexes. Some of these complexes have been used as catalysts in various reactions, e.g. $CpCo(CO)_2$ in trimerization of acetylenes and co-oligomerization of acetylenes and nitriles [1], and Cp_2TiCl_2 in reduction by Grignard reagents of ketones [2], esters [3], acetylenic compounds [4] and acids [5], in hydroalumination [6] or hydrogenation [7] of olefins. They have been also successfully employed in stoichiometric organic transformations, such as use of $Fe(CO)_2Cp$ species by Rosenblum [8], and use of Cp_2TiCl_2 to prepare π-allyltitanium complexes from dienes [9].

Use of alkyl-substituted cyclopentadienyl ligands in transition-metal complexes is increasing, especially of the pentamethylcyclopentadienyl (C_5Me_5 or Cp') ligand. Significant modifications of the physical properties and catalytic activities of transition-metal complexes may be brought about by replacement of hydrogen atoms in cyclopentadienyl ligands by alkyl groups. With these ligands present, steric hindrance around the metal may protect it from secondary reactions such as dimerization (self-polymerization) or from approach of bulky reagents. For example, $(CpRhCl)_n$ is insoluble in the main apolar solvents, and is reduced to the metal by hydrogen, whereas $(Cp'RhCl)_n$ is soluble in hydrocarbons and stable towards hydrogen [10]. In the titanium-catalyzed isomerization of olefins, the catalytic Cp'_2TiCl_2/naphthalene sodium system is far more selective than the Cp_2TiCl_2/naphthalene sodium system [11].

Cyclopentadienes bearing a chiral group (menthyl or neomenthyl) have been used as ligands [12] in titanium-promoted asymmetric hydrogenation of olefins [13], in the

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preparation of optically active carboxylic acids by carboxylation of π-allylic titanium complexes [14], and in the preparation of optically active aldehydes by nucleophilic attack on π-allylmolybdenum complexes [15].

Among the reactions known to produce monoalkylated cyclopentadienes, the most commonly used is the displacement of alkyl halides or tosylates by the cyclopentadienide (Cp^-) anion [16]. Addition of this anion to epoxides [17], formates or carbonates [18] yields functionally-substituted cyclopentadienes. Di-, tri-, or tetra-substituted cyclopentadienes are usually obtained by dehydration of the corresponding cyclopentenol [19].

Monosubstituted cyclopentadienide anions (or monosubstituted cyclopentadienes) are readily obtained by reactions of $LiAlH_4$ or alkyllithium compounds with 6,6-disubstituted fulvenes.

We describe below a method of synthesizing cyclopentadienes mono- or di-substituted by allylic groups, involving Pd-catalyzed reaction of allylic esters with a cyclopentadienide or a monosubstituted cyclopentadienide anion. This type of reaction also permits the preparation of monosubstituted indene by use of the indenide anion.

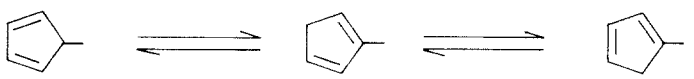
Results and discussion

Pd-catalyzed alkylation of various stabilized carbanions derived from organic acids of $pK_a < 18$ has been reported [20]. We expected that the stabilized cyclopentadienide anion (derived from the strongly acidic cyclopentadiene ($pK_a \sim 15$)) would be a convenient nucleophile for Pd-catalyzed substitution of allylic esters.

Synthesis of monosubstituted cyclopentadienes and indenes

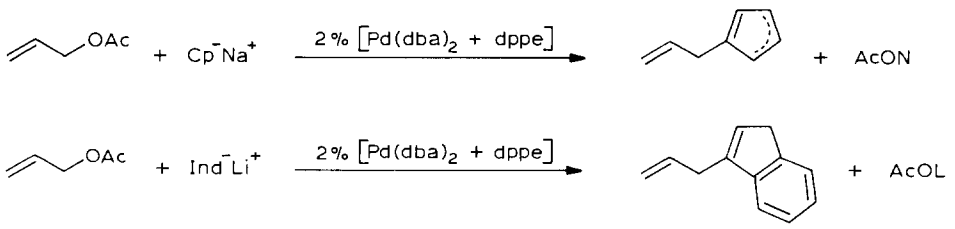
Table 1 outlines the results obtained in the Pd-catalyzed alkylation of 2-cyclohexen-1-yl and terpenyl acetates by the cyclopentadienide anion (see Scheme 1). The substitution took place without secondary reactions such as elimination of acetic acid to give 1,3 dienic products. Other side reactions, e.g. nucleophilic attack on the acetoxy group to give the corresponding alcohol, can be suppressed by use of a bulky carboxy group: thus allylic pivalates, which hindered towards nucleophilic attack, gave higher yields (cf. run 2 and 3, Table 1).

In the NMR spectra of compound Id to IVd, (Scheme 2), the signals from the bis allylic methylene group (δ 2.7 to 2.9 ppm) correspond with two protons. That means that the initially produced 5-substituted isomer (VI) is totally isomerized to VII and VIII under the conditions used *.



(VI) (VII) (VIII)

* Lower temperatures (-70 to -30°C) were usually needed to prevent double bond isomerization of the 5-substituted cyclopentadiene to the 1- and 2-substituted isomer [21].



dba = $PhCH{=}CHCOCH{=}CHPh$
dppe = $Ph_2PCH_2CH_2PPh_2$

SCHEME 1

Substrates III, IV leading to dissymmetrically substituted π-allylic intermediates were regiospecifically alkylated.

The 95/5 *cis/trans* mixture of optically active carvyl esters afforded a 95/5 diastereomeric mixture of racemic cyclopentadienes, revealing the occurrence of stereoselective reactions in the replacement of the OCOR group via a π-allylic intermediate. However, the stereochemistry of the reaction has not yet been determined.

The Pd-catalyzed substitution of allylic esters has advantages over conventional methods, such as substitution of allyl halides or tosylates by the cyclopentadienide anion. The conversion of cyclic allylic alcohols into halides is not always stereoselective [22], and attempted conversion into *p*-toluene sulfonates sometimes unsuccessful [23]. Moreover, the mild conditions employed (low reaction temperature, low phosphine to palladium ratio, and low catalyst concentration (1 to 2%)) ensured easy work-up and prevented rapid polymerization of the products.

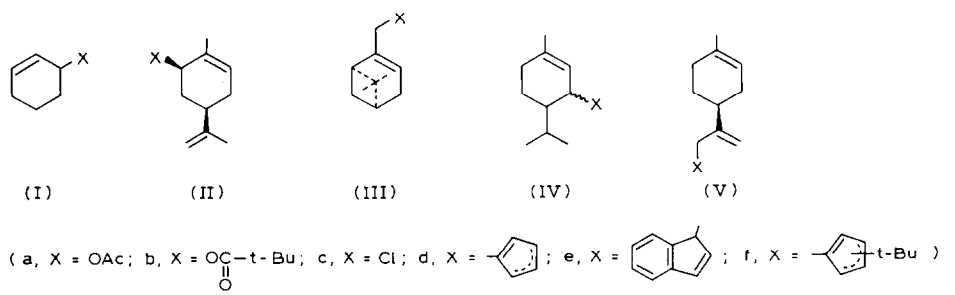
Indenide anion, although produced from a weaker carbon acid (pK_a 21) gave satisfactory yields of the product containing the more stable indenyl isomer (Table 2). The features of the regio- and stereochemical results are similar to those noted for the reactions of cyclopentadienide ion.

Synthesis of disubstituted cyclopentadienes

Allylation of monoalkylcyclopentadienes gave 1,2- and 1,3-regioisomers (Scheme 3).

The results listed in Table 3 show that the regioselectivity of the substitution depends on the steric demand of the alkylcyclopentadienide.

(*Continued on p. 398*)



SCHEME 2

TABLE 1

SYNTHESIS OF MONOSUBSTITUTED CYCLOPENTADIENES (SCHEME 1)

Run	Allylic substrate	Product	Kugelrohr [b] distillation B.p. (°C/mmHg)	^{1}H NMR chemical shifts δ ((ppm) in CCl_4)	Yield [a] (%)	Analysis (Found (calcd.) (%))	
						C	H
1	Ia	Id	55/0.3	1.35–2.10 (m,6H), 2.80 (s,2H) 3.10 (m,1H), 5.60 (s,2H), 5.85–6.45 (m,3H)	64	89.57 (90.41)	9.44 (9.59)
2	IIa	IId	100/0.1	1.95–2.15 (m,11H), 2.75 (m,2H), 2.90 (s,1H), 4.70 (s,2H), 5.50 (m,1H), 6.05–6.35 (m,3H)	69	89.69 (90.00)	9.96 (10.00)
3	IIb [c]	IId [d]			85		
4	IIIa	IIId [e]	80/0.1	0.75 (s,3H), 1.20 (s,3H), 1.95–2.40 (m,6H), 2.70–3.10 (m,4H), 5.20 (m,1H), 5.85–6.40 (m,3H)	72	89.18 (90.00)	9.96 (10.00)
5	IVa	IVd	140/1.5	0.7–2.50 (15H), 2.70–3.15 (m,3H), 5.55 (s,1H), 5.80–6.45 (m,3H)	56	89.37 (90.00)	10.87 (10.00)

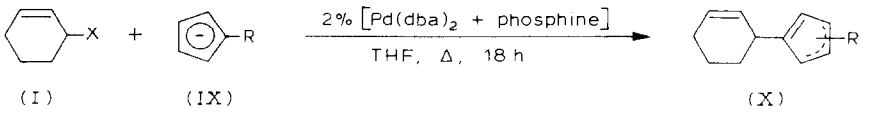
[a] Of isolated products. [b] Oven temperature. [c] 95/5 *cis/trans* mixture of optically active compounds. [d] 95/5 diastereomeric mixture of a racemic compound. [e] $[\alpha]_D^{20} - 31.5°$ (hexane, $c = 6.7$).

TABLE 2

SYNTHESIS OF MONOSUBSTITUTED INDENES (SCHEME 1)

Run	Allylic substrate	Product	Kugelrohr [b] distillation B.p. (°C/mmHg)	^{1}H NMR chemical shifts δ ((ppm) in CCl_4)	Yield [a] (%)	Analysis (Found (calcd.) (%)	
						C	H
1	Ia	Ie	110/0.5	1.55–1.90 (m,4H), 2.0–2.25 (m,2H), 3.3(s,2H), 3.50 (m,1H), 5.85 (s,2H), 6.25 (s,1H), 7.10–7.35 (m,2H), 7.35–7.55 (m,2H)	56	91.90 (91.84)	8.28 (8.16)
2	IIa [c]	IIe [d]	140/0.4	0.90–2.55 (m,11H), 3.4 (s,2H), 3.5–3.7 (m,1H), 4.7–4.9 (2H) 5.80 (s,1H), 6.30 (s,1H), 7.20–7.45 (m,2H), 7.45–7.65 (m,2H)	20	89.80 (91.20)	9.35 (8.80)
3	IIb [c]	IIe [d]			85		
4	IIIa	IIIe	145/0.4	0.80 (s,3H), 0.90–1.1 (m,2H), 1.25 (s,3H), 1.3–1.45 (m,1H), 1.9–2.3 (3H), 3.15–3.35 (4H)	52	91.42 (91.20)	8.95 (8.80)

[a] Of isolated products. [b] Oven temperature. [c] 95/5 *cis/trans* mixture of optically active compounds. [d] 95/5 diastereomeric mixture of a racemic compound.



(I) (IX) (X)

(b, X = OCO-t-Bu; c, X = Cl) (g, R = Me; h, R = i-Pr; i, R = t-Bu)

SCHEME 3

TABLE 3

REGIOSELECTIVITY IN THE ALKYLATION OF CYCLOHEXEN-3-YL CHLORIDE AND PIVALATE WITH ALKYLCYCLOPENTADIENIDE (SCHEME 3)

Run	Allylic substrate	Anion IX	Phosphine in catalyst	Product (regioisomeric ratio) [b]		Yield [a]
1	Ic	IXh	no catalyst	Xh	(54/46)	75 [c]
2	Ib	IXh	PPh_3	Xh	(61/39)	51
3	Ib	IXh	P(*o*-tolyl)$_3$	Xh	(75/25)	40
4	Ib	IXg	PPh_3	Xg	(58/42)	44
5	Ib	IXi	PPh_3	Xi	(>100/1)	52

[a] Of isolated product. [b] Tentatively assigned as 1.3/1.2 ratio. [c] Reaction at room temperature.

The Pd-catalyzed allylation of i-propylcyclopentadiene with 2-cyclohexen-1-yl pivalate (IXb) was more regioselective than allylation with the corresponding chloride (Xc). This may indicate a greater steric interaction of the cyclopentadienide anion with the bulky allylic palladium intermediate than with the allylic chloride. The regioselectivity was also improved by the use of a bulkier phosphine ligand such as tri-(*o*-tolyl)-phosphine.

The reaction with t-butyl cyclopentadienide (IXi) was regioselective with respect to the allylic ester (reaction at the less substituted allylic end) (Table 4, run 3), and also cyclopentadiene (to give the 1,3-disubstituted cyclopentadiene). The reaction was also stereoselective (Table 4, run 4).

Concluding remarks

The Pd-catalyzed alkylation of allylic esters is a convenient method of producing substituted cyclopentadienes, indenes, and 3-substituted t-butylcyclopentadienes. The substitution is stereoselective, and permits the preparation of optically active cyclopentadienes and indenes, for use as chiral ligands. Furthermore, 1,3-substituted cyclopentadienes and substituted indenes, upon coordinated to a metal would yield chiral complexes.

Experimental

Materials

All reactions were run under dry nitrogen, and solutions were transferred by Schlenk tube techniques. Diisopropylamine was refluxed over calcium hydride and

TABLE 4

SYNTHESIS OF MONSUBSTITUTED t-BUTYLCYCLOPENTADIENES

Run	Allylic substrate	Product	Kugelrohr distillation B.p. (°C/mmHg) [a]	^{1}H NMR chemical shifts δ ((ppm) in $CDCl_3$)	Yield [b] (%)	Analysis (Found (calcd.) (%))	
						C	H
1	Ib	If	105/0.4	1.13 (s,9H), 1.4–2.1 (6H), 2.80–2.9 (m,2H), 3.2 (m,1H), 5.6–5.8 (2H), 5.95–6.2 (2H)	52	88.95 (89.11)	10.77 (10.89)
2	IIb [c]	IIf [d]	130/0.5	1.14 (s,9H), 1.2–2.2 (m,11H), 2.7–3.25 (3H) 4.7 (s,2H), 5.4–5.6 (m,1H), 5.7–6.2 (2H)	42	89.12 (89.06)	10.81 (10.94)
3	IIIb	IIIf	120/0.4	0.80 (s,1H), 1.15 (s,9H), 1.24 (s,3H), 1.91–2.5 (m,4H), 2.7–3.1 (m,4H), 5.2–5.3 (m,1H) 5.7–6.3 (m,2H)	41	89.11 (89.06)	10.75 (10.94)
4	Va	Vf	140/0.4	1.12 (s,9H), 1.35–2.3 (m,10H), 2.7–3.2 (4H) 4.7–4.9 (d,2H), 5.35 (dd,1H), 5.8–6.3 (2H)	39	88.95 (89.06)	10.98 (10.94)

[a] Temperature of the oven is shown. [b] Of isolated product. [c] 95/5 *cis/trans* diastereoisomeric mixture. [d] 95/5 diastereomeric mixture (unknown relative configuration).

distilled at atmospheric pressure. All solvents were freshly distilled and stored under nitrogen. They were degassed immediately before use. THF (Aldrich) was refluxed over benzophenone ketyl under nitrogen. Butyllithium, purchased from Aldrich as a 1.6 *M* hexane solution was titrated using Kofron's method involving diphenylacetic acid [24]. Palladium chloride was obtained from "La Compagnie des Métaux Précieux". $Pd(dba)_2$(dba = dibenzylidene acetone) was prepared by a published procedure [25]. The abbreviation dppe denotes 1,2-(bis-diphenylphosphino)-ethane.

2-Cyclohexen-1-ol, (−)-myrtenol, and (+)-limonen-10-ol were purchased from Aldrich. (−)-*cis*-carveol (95% *cis*) was prepared by $LiAlH_4$ reduction of l-carvone in ether. Acetates were obtained by reaction of acetic anhydride in triethylamine, with DMAP (4-dimethyl-aminopyridine) as a catalyst (2%) [26]. Pivalates were made from pivaloylchloride in pyridine. Cyclopentadiene and methylcyclopentadiene were obtained by thermolysis of their corresponding dimers.

Analysis

Liquid products were usually purified by Kugelrohr distillation, with a Büchi oven, model GKR-50, the temperature of the oven being recorded. Reactions were monitored by thin layer chromatography (TLC) on plastic-backed sheets coated with silica-gel (Merck, Kieselgel 60, F-254, Art. 6753). Flash chromatography was carried out on silica-gel (Merck, Kieselgel 60, 230–400 mesh, Art. 9385). Vapor phase chromatographic analysis (VPC) were performed with a Fractovap GI (Erba Science) gas chromatograph equipped with a 3 m column packed with 3% OV-17 on Chromosorb WHP 100–120 mesh (column A) or a 15 m OV-1 coated glass capillary column (column B), and a flame-ionization detector. Proton (^1H) NMR spectra were recorded in the indicated solvent on a Perkin–Elmer R 32 (at 90 MHz) instrument. Chemical shifts were measured relative to tetramethylsilane (TMS, δ 0.00). Mass spectra (MS) were obtained on a Nermag R-10-10 apparatus at 70 eV, coupled to a gas-chromatograph (Girdel) equipped with a 25 m fused silica capillary column coated with CP SIL 5. Microanalyses were carried out by the Service Central de Microanalyse, I.C.S.N., Gif-sur-Yvette.

General procedure for the preparation of substituted cyclopentadienes

A solution of the allylic ester (3.6 mmol), $Pd(dba)_2$ (0.036 mmol) and dppe (0.036 mmol) in THF (5 ml) was stirred for 10 min, and a solution of sodium cyclopentadienide (4.0 mmol) in THF (10 ml) (prepared by reaction of cyclopentadiene (6.0 mmol) and sodium (4.0 mmol) (as a 50% dispersion in paraffin)) was added. After 24 h stirring at room temperature, water (200 ml) was added. The crude mixture was extracted with ether (3 × 50 ml) and the extract was dried ($MgSO_4$) and evaporated. The oily residue was purified by column chromatography on silica gel (hexane as eluent) followed by Kugelrohr distillation. NMR data are listed in Table 1; the signals are generally broad owing to the presence of double bond regioisomers in the cyclopentadiene ring.

Preparation of substituted indenes

The procedure described as above was used but with the sodium cyclopentadienide reagent replaced by indenyllithium, prepared by addition of equimolecular amount of n-BuLi in hexane to a solution of freshly distilled indene in THF under nitrogen at 0°C.

Regioselectivity in the substitution of cyclohexene-2-yl derivatives by methyl, isopropyl, and t-butylcyclopentadienide anion

The lithium methylcyclopentadienide anion was made by reaction of equimolecular amounts of BuLi and methylcyclopentadiene in THF. Lithium isopropylcyclopentadienide was prepared by reaction of equimolecular amounts of $LiAlH_4$ and 6,6-dimethylfulvene in ether. After isolation it was redissolved in THF.

The subsequent reactions were carried out as described above.

When methyl and isopropyl cyclopentadienide anions were used, two regioisomers were detected (CPV, column A) in the products and these were tentatively identified as the 1,3- and 1,2-isomers. These isomers were also distinguished by NMR in IXh, there were two doublets for the i-Pr group, δ 1.13 (J 6 Hz), isomer A (1,2-regioisomer) and δ 1.09 (J 6 Hz), isomer B (1,3-regioisomer). The isomers showed different intensity patterns in their MS spectra. MS: m/e (relative intensity) isomer A 188(35), 173(13), 145(100), 81(54); isomer B 188(91); 173(65), 145(95), 81(100).

Further analysis of the spectra of the regioisomers obtained from the isopropylcyclopentadienide anion (CPV, column B) revealed that each signal was split into two or three peaks, attributed to regioisomers differing in the positions of the double bonds of the cyclopentadiene unit.

Preparation of substituted t-butylcyclopentadienes

To 0.536 g (5 mmol) 6,6-dimethylfulvene in ether (10 ml), 5 mmol of a standardized (ca. 1.3 M) solution of MeLi in ether were added at 0°C under nitrogen. The ether was decanted off and the white solid was washed with fresh ether, dried, and dissolved in THF (10 ml). The solution was added to a solution of allylic acetate (3 mmol), $Pd(dba)_2$ (34.5 mg, 0.06 mol) and dppe (24 mg, 0.06 mol) in THF (5 ml). The mixture was stirred for 18 h at 40°C, cooled, and poured into saturated aqueous ammonium chloride, and extracted with hexane (3 × 50 ml). The extract was dried ($MgSO_4$), then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane as eluent) followed by Kugelrohr distillation.

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