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PALLADIUM CATALYZED DOUBLE HECK ARYLATION OF CYCLOPENTENE

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Abstract: A convenient synthesis of 1,3-diarylcyclopentenes is described via a palladium catalyzed double Heck arylation of cyclopentene with aromatic halides.

Preparation of 1,3-diarylcyclopentane derivatives **1**, carbon isosteres of the known Platelet Activating Factor (PAF) antagonists 2,5-diaryltetrahydrofurans[1], requires 1,3-diarylcyclopentenes **2** as key intermediates. The reported[2] method of synthesis of 1,3-diarylcyclopentenes involves several steps proceeding via arylgrignard reagents, which are often prone to dimerization to biphenyls[3].

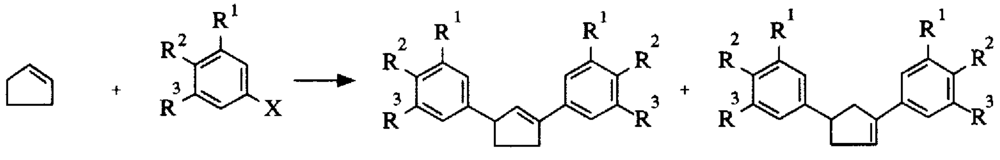

1


2

In this letter we report a convenient synthesis of these intermediates by a palladium catalyzed double Heck arylation of cyclopentene with aromatic halides. Although palladium catalyzed arylation of cyclopentene with aromatic halides to furnish 3-arylcyclopentenes has been reported[4,10], the double Heck arylation of cycloalkenes is unknown.

The results with several aromatic halides are listed in Table 1. Treatment of cyclopentene with 2.3 equivalents of aromatic halide under classical Heck reaction conditions[5] gave 1,3-diarylcyclopentenes in excellent yields [6] (Table 1, Entries 1, 2, and 3) as mixtures of double bond isomers **2** and **3**. Analysis of the ^{1}H-NMR spectra of the isolated products suggested a 2:1 ratio of the desired **2** to the undesired **3** based on characteristic multiplicities and chemical shifts for the benzylic methine protons[7]. This was confirmed by HPLC and ^{1}H-NMR comparison with authentic **2** and **3** (R^1=R^2=R^3=OMe)[8].

Table 1. Palladium Catalysed Double Heck Arylation of Cyclopentene.



2 3

Entry	Aryl Halide R^1	R^2	R^3	X	Method	Products Ratio^a 2	3	Isolated Yield (%)
1	OMe	OMe	OMe	Br	A	2	1	83
2	OMe	OMe	H	Br	A	2	1	93
3	H	OMe	H	Br	A	2	1	88
4	OMe	OMe	OMe	I	B	>95	2.2	82
5	H	OMe	H	I	B	>95	(b)	84
6	H	H	H	I	B	>95	(b)	85
7	OMe	H	OMe	I	B	>95	(b)	82

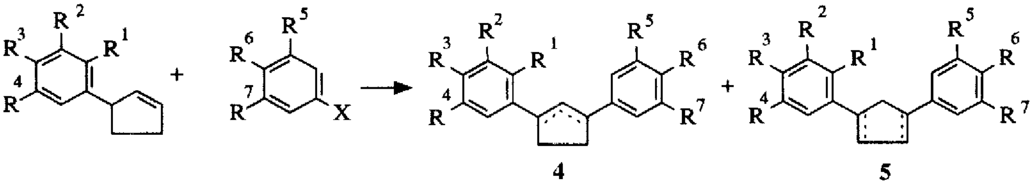
Method A: A mixture of cyclopentene (1 equiv.), aryl halide (2.3 equiv.), Pd $(OAc)_2$ (0.02 equiv.), tri-*o*-tolylphosphine (0.08 equiv.), Et_3N (2.6 equiv.), and CH_3CN (0.6 ml/mmol) was heated at 100°C in a sealed tube for 48 hrs. Method B: A mixture of cyclopentene (1 equiv.), aryl halide (2.3 equiv.), $Pd(OAc)_2$ (0.025 equiv.), n-Bu_4NCl (2.3 equiv.), KOAc (6.9 equiv.), and dry DMF (3.5 ml/mmol) was heated at 80°C for 48 hrs. with stirring under an atmosphere of nitrogen.

[a] As determined by HPLC and/or ^{1}H-NMR of the isolated product. [b] None detected by ^{1}H-NMR.

In an attempt to improve this ratio in favor of the desired 1,3-diarylcyclopentenes, the double Heck arylation was carried out under milder solid-liquid Phase Transfer Catalysis (PTC) conditions reported by Jeffery[9] and Larock[10]. As indicated in Table 1 (Entries 4-7), the reaction with aromatic iodides proceeded in excellent yields[6] although aromatic bromides failed to react. ^{1}H-NMR analysis of the isolated products indicated only the desired 1,3-diarylcyclopentenes 2. HPLC analysis of Entry 4 confirmed the presence of 2.2% of the isomeric 3. Because alkene isomerization may arise from readdition-elimination of Pd-H species[4], probably such a process is suppressed under PTC conditions leading to the observed selectivity in contrast to that found under classical Heck conditions.

1,3-Diarylcyclopentenes bearing unsymmetrical aromatic groups can be prepared by conducting a Heck arylation stepwise. The results of this previously unknown Heck arylation of 3-arylcyclopentenes[10] with several aromatic bromides under classical Heck conditions are listed in Table 2 (Entries 1-5). These conditions allow use of the readily available aromatic bromides which do not react under PTC conditions. This reaction affords in good yield

Table 2. Palladium Catalysed Heck Arylation of 3-Arylcyclopentene



Entry	3-Arylcyclopentene R^1	R^2	R^3	R^4	Aryl Halide R^5	R^6	R^7	X	Method (hrs)	Isolated Yield (%)
1	H	OMe	OMe	OMe	H	CO_2Me	H	Br	A(24)	75[a]
2	H	OMe	OMe	OMe	H	OMe	H	Br	A(36)	59[a]
3	H	OMe	OMe	OMe	OMe	OCH_2Ph	OMe	Br	A(41)	80[a]
4	OMe	OMe	OMe	H	H	H	H	Br	A(18)	56[a]
5	OMe	OMe	OMe	H	OMe	OMe	OMe	Br	A(19)	62[a]
6	H	OMe	OMe	OMe	H	OMe	H	I	B(24)	68[b]

Method A: A mixture of 3-arylcyclopentene (1 equiv.), aryl halide (1 equiv.), $Pd(OAc)_2$ (0.01 equiv.), tri-o-tolylphosphine (0.04 equiv.), Et_3N (1.3 equiv.), and CH_3CN (0.5 ml/mmol) was heated at 100°C in a sealed tube. Method B: A mixture of 3-arylcyclopentene (1 equiv.), aryl iodide (1 equiv.), $Pd(OAc)_2$ (0.025 equiv.), n-Bu_4NCl (1 equiv.), KOAc (3 equiv.), and dry DMF (3.5 ml/mmol) was heated at 80°C.

[a]Ratio of regioisomers in 4 and ratio of regioisomers in 5 was not determined. [b]None of 5 was detected by ^{1}H-NMR.

an inseparable mixture of double bond isomers 4 and 5 in approximately a 1.5:1 ratio. Reaction of 3-(3,4,5-trimethoxyphenyl)cyclopentene with 4-iodoanisole under PTC conditions (Table 2, Entry 6) gave only 4. The ratio of the two possible double bond isomers could not be determined by ^{1}H-NMR. This is in sharp contrast to classical Heck conditions which gave a mixture of 4 and 5 in a 1.5:1 ratio (Table 2, Entry 2).

1-(3,4,5-Trimethoxyphenyl)cyclopentene[11] reacted slowly under classical Heck conditions to furnish in poor yield (20% in 40 hours.) 1,5-bis(3,4,5-trimethoxyphenyl)cyclopentene. This sluggish reactivity of the 1-arylcyclopentene explains the absence of any 1,5-diarylcyclopentenes during the double Heck arylation. Any 1-arylcyclopentene produced after the initial arylation reaction reacts too slowly to compete with the 3-arylcyclopentene.

Thus, a double Heck arylation of cyclopentene with aromatic halides provides a convenient method for the preparation of 1,3-diarylcyclopentenes containing symmetrical aromatic groups. Performing the reaction under phase transfer conditions increased the selectivity favoring the formation of one olefin regioisomer. This is in contrast with the results obtained under classical Heck conditions. 1,3-Diarylcyclopentenes bearing unsymmetrical aromatic groups can be prepared by a Heck reaction of 3-arylcyclopentenes with aromatic halides.

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References and Notes

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6. All the compounds gave appropriate ^{1}H-NMR, mass spectral, or elemental analysis data.
7. In 1,3-diarylcyclopentenes (2) it appears as a multiplet at δ4.02 while in 1,4-diarylcyclopentenes (3) it is a quintet at δ3.6.
8. Unpublished results. 2 and 3 were prepared by dehydration of 2,5-Bis(3,4,5-trimethoxyphenyl)cyclopentane-1-ol and 2,4-bis(3,4,5-trimethoxyphenylcyclopentane-1-ol respectively.
   1,3-Bis(3,4,5-trimethoxyphenyl)cyclopentene (in Structure 2 Table 1, R^1=R^2=R^3=OMe): ^{1}H-NMR (CDCl$_3$, δ)1.95(m,1H), 2.6(m,1H), 2.85(m,1H), 4.02(m,1H,-CH-Ar), 6.15(d,1H,-CH=).
   1,4-Bis(3,4,5-trimethoxyphenyl)cyclopentene (in Structure 3 of Table 1, R^1=R^2=R^3=OMe): ^{1}H-NMR (CDCl$_3$, δ) 2.5-3.28 (m, 4H), 3.6 (quintet, 1H,-CH-Ar), 6.15 (bs, 1H, -CH=).
9. T. Jeffery, J. Chem. Soc., Chem. Commun., 1287 (1984).
10. R.C. Larock and B.E. Baker, Tetrahedron Lett., 29, 905 (1988) and references cited therein. (This paper appeared while our work was in progress.)
11. Prepared by Heck arylation of cyclopentene with 3,4,5-trimethoxyiodobenzene, Pd(OAc)$_2$, Et$_3$N and CH$_3$CN (see Reference 4 and references cited therein).

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