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A NEW PALLADIUM CATALYZED SYNTHESIS OF CIS,EXO-2,3-DIARYLSUBSTITUTED BICYCLO[2.2.1]HEPTANES OR BICYCLO[2.2.1]HEPT-2-ENES

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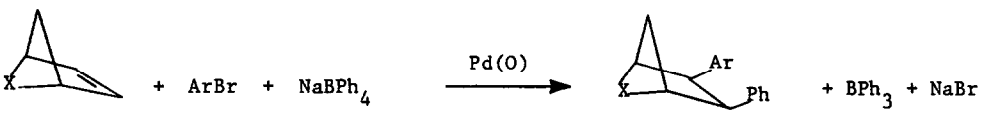
Abstract - The title bicycloheptanes or bicycloheptenes, containing a phenyl group and an aryl group in 2,3 positions, are obtained by oxidative addition of aryl bromides to palladium(0), followed by double bond insertion and coupling with a phenyl group of tetraphenyl borate anion.

In previous papers we described the synthesis of bicycloheptanes or bicycloheptenes, containing adjacent alkynyl and aliphatic or aromatic chains.[1]

We now report a new high yield, one pot synthesis of 2,3-diarylsubstituted derivatives, according to equation 1:



I (X = $-CH_2CH_2-$)
II (X = -CH=CH-)
III (X = $-CH_2CH_2-$)
IV (X = -CH=CH-)

(1)

The reaction requires mild conditions and can be carried out in a very simple way. Thus the reagents and the catalyst ($[Pd(PPh_3)_4]$) are mixed under nitrogen in a solvent such as anisole and stirred at 80°C for some hours. Compound III or IV are isolated in satisfactory yields, following usual procedures. Results are reported in the Table. A secondary reaction, leading to asymmetric diaryls, also occurs, according to equation 2.

$$ArBr + NaBPh_4 \longrightarrow ArPh + BPh_3 + NaBr \qquad (2)$$

Yields drop to low values (less than 20%) with bromopyridines. The reaction can also be applied to other organic bromides. For example, E-bromostyrene gives a 92% yield of the corresponding 2-phenyl-3-β-styrylbicyclo[2.2.1]heptane. Other reactive bromides are the allylic or benzylic ones, but yields are generally low.

The product stereochemistry is cis, exo, even in the case of bicycloheptadiene. The latter was shown to be phenylated endo by sodium tetraphenylborate in a palladium(II) complex.[2] In our case phenylation occurs exo because an exo C-Pd bond, formed by cis, exo double bond insertion, is replaced by a C-Ph bond.

Table. Reaction of aromatic bromides with I or II, $Na[BPh_4]$ and $[Pd(PPh_3)_4]$ as catalyst (molar ratio 1:1.2:1:0.005) in anisole (catalyst concentration 1.5-2.5 M) at 80°C for 18 h.

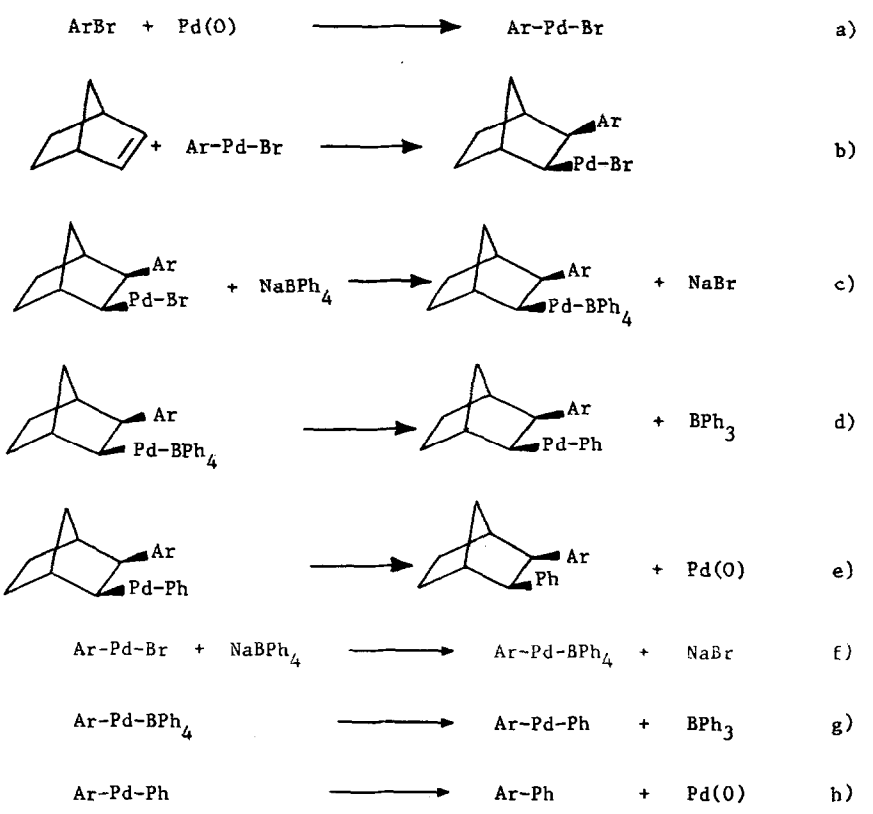
Substrate	Aromatic bromide RBr	Yield[a] of III or IV (%)
I	R = Ph	95
	o-Tolyl	93
	m-Tolyl	83
	p-Tolyl	93
	p-Anisyl	91
	p-Nitrophenyl	74
	o-Thienyl	85
II[b]	p-Tolyl	63

[a] on the bromide; [b] 1.6 mmol of II.

The catalytic efficiency approaches 200 mol of III per mol of catalyst. No attempt was made to optimize it, however.

The proposed mechanism is shown in the Scheme for I (non reactive ligands are omitted).

The synthesis includes the following steps: a) oxidative addition of aryl bromides to palladium(0) complexes; b) bicycloheptene or bicycloheptadiene insertion; c) bromide metathesis with tetraphenylborate anion; d) cleavage of a phenyl group of the latter by palladium with formation of BPh_3; and e) C-C coupling of the palladium-bonded phenyl and cycloaliphatic rings. Coupling of an aryl group with the phenyl group without double bond insertion (f,g,h) leads to the secondary reaction (2).



Scheme

The method here described makes accessible bicycloheptane or bicycloheptene compounds, containing two different aromatic groups. We recently became aware of another method,[3] which is related to our original work,[1] but is based on the use of organotin compounds to effect C-C coupling. This method was also applied to the addition of two phenyl groups to the bicycloheptene double bond (compound III, R,R' = C_6H_5). Compared with our method, which uses the commercially available sodium tetraphenylborate, the yield was lower (60% against 95%), however.

Stilbenes, containing different aromatic groups, can also be obtained from diarylbicycloheptenes by a retro-Diels Alder reaction (thermal treatment in a silica tube at 500°C). These are interesting products, which may be used in the field of optical brightening and of non linear optics.

We believe that the synthesis here described offers a simple and efficient way to the preparation of a wide range of useful products.

Experimental

Starting materials were all commercially available (C. Erba, Aldrich and Strem). Products were isolated by preparative flash chromatography and analyzed by GLC on a methylsilicone (OV-101 stationary phase) capillary column with internal standard. Mass spectra were recorded on a Finnigan 1020 instrument at 70 eV. ^{1}H and ^{13}C NMR spectra were aken in $CDCl_3$ on CXP200 and AC100 Bruker spectrometers at 200 and 25.1 MHz, respectively. Chemical shifts are in ppm from TMS as internal reference. Melting points were taken on a Kofler apparatus and are uncorrected.

General Procedure

The following procedure, referring to the preparation of III (R,R' = C_6H_5), is representative. The aromatic bromide, 0.6 mmol, bicycloheptene or bicycloheptadiene, 0.72 mmol, sodium tetraphenylborate, 0.6 mmol, and tetrakis(triphenylphosphine)palladium, 0.003 mmol, were stirred in anisole, 2 ml, at 80°C for 18 hours under nitrogen. The products were isolated as indicated above.

Retro-Diels Alder reaction.

The product (IV) was sublimed *in vacuo* (1 mm Hg) into a horizontal silica tube, heated at 500°C with an external electric furnace, and the resulting stilbene was collected in a liquid air trap, according to the general procedure described in the literature.[4]

Properties of products

III (R,R' = C_6H_5),[5] 2,3-diphenylbicyclo[2.2.1]heptane, m.p. 47.0-47.5°C (hexane), M^+ 248; ^{1}H NMR: δ 7.05-6.78 (m, 10 aromatic H), 3.28 (d, $J_{2,3-7\ anti}$ 1.5 Hz, 2H, H(2), H(3)), 2.59 (br s, 2H, H(1), H(4)), 2.25 (d, further split, J 10.0, 1.8 Hz, 1H, H(7 *syn*)), 1.81-1.67 (m, 2H, H(5 *exo*), H(6 *exo*)), 1.58-1.42 (m, 3H, H(5 *endo*), H(6 *endo*), H(7 *anti*)); ^{13}C NMR: δ 142.8, 128.5, 127.1, 124.8 (aromatic C), 54.6 (d, C(2), C(3)), 41.8 (d, C(1), C(4)), 37.1 (t, C(7)), 30.6 (t, C(5), C(6)).

III (R = *o*-$CH_3C_6H_4$, R' = C_6H_5), m.p. 41.0-41.5°C (hexane), M^+ 262; ^{1}H NMR: δ 7.24 (dd, J 6.9, 1.0 Hz, 1H), 7.05-6.76 (m, 8 aromatic H), 3.36, 3.25 (2dd, J 9.6, 1.4 Hz, 2H, H(2). H(3)), 2.67, 2.37 (2 br s, 2H, H(1), H(4)), 2.32 (d, further split, J 10.0, 1.9 Hz, 1H, H(7 *syn*)), 2.05 (s, 3H, CH_3), 1.80-1.69 (m, 2H, H(5 *exo*), H(6 *exo*)), 1.57-1.42 (m, 3H, H(5 *endo*), H(6 *endo*), H(7 *anti*)); ^{13}C NMR: δ 143.2, 141.4, 136.3, 129.6, 128.7, 127.0, 126.1, 125.3, 125.2, 55.3, 50.9, 44.4, 41.1, 36.9, 31.0, 30.9, 20.5.

III (R = m-$CH_3C_6H_4$, R' = C_6H_5), m.p. 39.0-39.5°C (hexane), M^+ 262; ^1H NMR: δ 7.00-6.60 (m, 9 aromatic H), 3.25 (d, $J_{2,3-7\ anti}$ 1.4 Hz, 2H, H(2), H(3)), 2.58 (br s, 2H, H(1), H(4)), 2.24 (d, further split, J 10.0, 1.7 Hz, 1H, H(7 syn)), 2.09 (s, 3H, CH_3), 1.80-1.66 (m, 2H, H(5 exo), H(6 exo)), 1.58-1.40 (m, 3H, H(5 endo), H(6 endo), H(7 anti)); ^{13}C NMR: δ 143.0, 142.8, 136.5, 129.6, 128.6, 127.2, 125.6, 125.5, 124.9, 54.8, 42.0, 41.9, 37.3, 30.7, 21.3.

III (R = p-$CH_3C_6H_4$, R' = C_6H_5), m.p. 61.0-61.5°C (hexane), M^+ 262; ^1H NMR: δ 7.05-6.70 (m, 9 aromatic H), 3.25 (d, $J_{2,3-7\ anti}$ 1.2 Hz, 2H, H(2), H(3)), 2.58, 2.54 (2 partially overlapping br s, 2H, H(1), H(4)), 2.22 (d, further split, J 10.0, 1.9 Hz, 1H, H(7 syn)), 2.13 (s, 3H, CH_3), 1.80-1.68 (m, 2H, H(5 exo), H(6 exo)), 1.54-1.40 (m, 3H, H(5 endo), H(6 endo), H(7 anti)); ^{13}C NMR: δ 142.9, 139.7, 134.1, 128.5, 128.3, 127.8, 127.1, 124.7, 54.5, 54.3, 42.1, 41.8, 37.0, 30.5, 20.7.

III (R = p-$CH_3OC_6H_4$, R' = C_6H_5), m.p. 82.0-82.5°C (hexane), M^+ 278; ^1H NMR: δ 7.02-6.80 (m, 5 aromatic H), 6.81-6.72, 6.55-6.46 (AA'BB' system), 3.65 (s, 3H, OCH_3), 3.24 (d, $J_{2,3-7\ anti}$ 1.2 Hz, 2H, H(2), H(3)), 2.59, 2.53 (2br s, 2H, H(1), H(4)), 2.21 (d, further split, J 10.0, 1.9 Hz, 1H, H(7 syn)), 1.80-1.66 (m, 2H, H(5 exo), H(6 exo)), 1.57-1.40 (m, 3H, H(5 endo), H(6 endo), H(7 anti)); ^{13}C NMR: δ 156.7, 142.9, 135.0, 129.3, 128.4, 127.1, 124.7, 112.5, 54.8, 54.5, 53.8, 42.1, 41.7, 36.9, 30.5.

III (R = p-$NO_2C_6H_4$, R' = C_6H_5), m.p. 96.0-96.5°C (hexane), M^+ 293; ^1H NMR: δ 7.86-7.77, 7.06-6.98 (AA'BB' system), 6.96-6.80 (m, 5 aromatic H), 3.36 (d, $J_{2,3-7\ anti}$ 1.1 Hz, 2H, H(2), H(3)), 2.64, 2.60 (2 partially overlapping br s, 2H, H(1), H(4)), 2.23 (d, further split, J 10.3, 1.9 Hz, 1H, H(7 syn)), 1.85-1.72 (m, 2H, H(5 exo), H(6 exo)), 1.60 (br d, J 10.3 Hz, 1H, H(7 anti)), 1.58-1.47 (m, 2H, H(5 endo), H(6 endo); ^{13}C NMR: δ 151.2, 145.3, 141.9, 129.3, 128.4, 127.7, 125.6, 122.5, 54.8, 54.7, 41.9, 41.8, 37.4, 30.6, 30.5.

III (R = o-thienyl, R' = C_6H_5), m.p. 59.0-59.5°C (hexane), M^+ 254; ^1H NMR: δ 7.15-6.90 (m, 5 aromatic H), 6.83 (dd, J 5.0, 1.0 Hz, 1H, S-CH), 6.62 (dd, J 5.0, 3.5 Hz, 1H, S-CH-CH), 6.48 (br d, J 3.5 Hz, 1H, S-C-CH), 3.56, 3.22 (2br d, J 9.6 Hz, 2H, H(2), H(3)), 2.67, 2.54 (2br s, 2H, H(1), H(4)), 2.26 (d, further split, J 10.2, 1.8 Hz, 1H, H(7 syn)), 1.83-1.68 (m, 2H, H(5 exo), H(6 exo)), 1.60-1.38 (m, 3H, H(5 endo), H(6 endo), H(7 anti)); ^{13}C NMR: δ 147.0, 142.5, 128.5, 127.4, 125.4, 125.3, 124.6, 122.9, 54.4, 51.0, 44.6, 41.5, 37.0, 30.6, 30.2.

III (R = β-styryl, R' = C_6H_5), M^+ 274; ^1H NMR: δ 7.35-7.00, 6.97-6.82 (2m, 8+2 aromatic H), 6.19 (d, J 15.7, 1H, =CH-Ph), 5.41 (dd, J 15.7, 9.5 Hz, 1H, =CH), 3.05 (d, J 9.1 Hz, 1H, H(2)), 2.76 (dd, J 9.1, 9.5 Hz, 1H, H(3)), 2.64, (br s, 1H, H(1)), 2.24 (br s, 1H, H(4)), 1.94 (br d, J 10.0 Hz, 1H, H(7 syn)), 1.76-1.60 (m, 2H, H(5 exo), H(6 exo), 1.50-1.30 (m, 3H, H(5 endo), H(6 endo), H(7 anti)); ^{13}C NMR: δ 142.7, 138.0, 133.8, 128.3, 128.2, 128.1, 127.7, 126.3, 125.7, 125.1, 52.6, 52.0, 43.1, 40.8, 35.3, 30.6, 29.0.

IV (R = p-$CH_3C_6H_4$, R' = C_6H_5), 5-p-tolyl-6-phenylbicylo[2.2.1]hept-2-ene, m.p. 46.0-46.5°C (hexane), m/e 194 (M^+-66); ^{1}H NMR: δ 7.10-6.70, (m, 9 aromatic H), 6.41 (m, H(2), H(3)), 3.16 (d, $J_{5,6-7\ anti}$ 1.6 Hz, 2H, H(5), H(6)), 3.10, 3.05 (2 partially overlapping br s, 2H, H(1), H(4)), 2.28 (br d, J 8.7 Hz, 1H, H(7 anti to the double bond), 2.14 (s, 3H, CH_3), 1.74 (d, further split, J 8.7, 1.6 Hz, 1H, H(7 syn to the double bond)); ^{13}C NMR: δ 142.8, 139.6, 139.5, 134.4, 128.8, 128.6, 128.1, 127.4, 125.1, 49.0, 48.9, 47.5, 47.1, 45.7, 20.8. Hydrogenation of IV (R = p-$CH_3C_6H_4$, R' = C_6H_5), with Pd/C gives III (R = p-$CH_3C_6H_4$, R' = C_6H_5).

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References and Footnotes.

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5. Although this compound has been already described,[3] additional data are reported here.