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OXIDATIVE ADDITION, INSERTION, CYCLIZATION AND AMINATION IN A PALLADIUM-CATALYZED SEQUENCE

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Summary

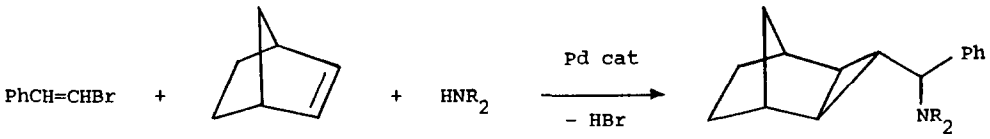
In a catalytic process styryl bromide undergoes oxidative addition to palladium(0) complexes, followed by insertion of bicyclo[2.2.1]hept-2-ene and cyclization to a condensed cyclopropane ring. The process is terminated by C–N coupling with primary or secondary amines.

Introduction

In the course of our studies on metal-catalyzed organic syntheses, involving several steps in sequence, we described methods for inducing double bond insertions into metal–carbon bonds [1]. An irreversible step, driving preceding reversible steps towards the final product, is provided by H elimination or uptake or by C–C coupling. The search for nucleophilic reagents, able to cleave a Pd–C bond by coupling, led us to examine primary and secondary amines. Of the latter, cycloaliphatic amines turned out to be the most efficient terminating agents.

Results and discussion

Styryl bromide reacts with bicyclo[2.2.1]hept-2-ene and amines according to eq. 1, where R_2 can be alkyls, also joined together in a cycloaliphatic ring:



(I)

The reaction takes place under mild conditions upon heating the reagents in

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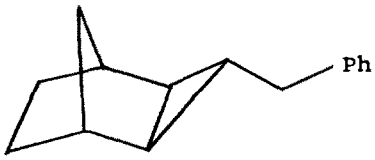
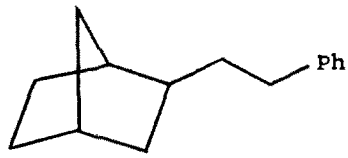
anisole at 80–105 °C under N_2 in presence of $Pd(PPh_3)_4$ as catalyst and of alkali salts of carboxylic acids to favor the insertion process.

The structure of the product was assigned on the basis of spectrochemical data (see Experimental) and of chemical evidence. The latter was provided by Pd-catalyzed hydrogenolysis of the C–N bond, leading to the known [2] compound II, together with minor amounts of a compound III resulting from further hydrogenolytic cyclopropane ring cleavage.



(II)

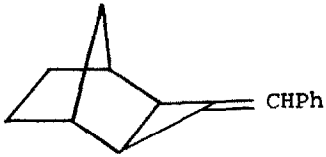


(III)

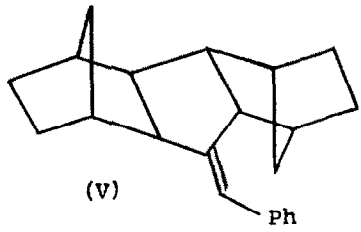
As shown in Table 1, large differences were observed in the series of homologous aliphatic amines. Dimethylamine gave a moderate reaction but diethylamine gave virtually no reaction and higher homologues reacted only to a very slight extent.

Primary amines such as n-butylamine gave satisfactory reactions but the products were varied and not determined quantitatively. Aromatic or heterocyclic amines were found to be unreactive.

Beside some unidentified products resulting from reactions of bromostyrene not involving bicycloheptene, the main by-products containing bicycloheptene were IV and V.



(IV)



(V)

Hydrogenation of IV on Pd/C gave III. Compound IV resulted from cyclopropane ring closure and H elimination after bicycloheptene insertion. Compound V is

TABLE 1

REACTION OF *E*-β-BROMOSTYRENE WITH BICYCLO[2.2.1]HEPT-2-ENE AND AMINES IN 1/1/2–3 MOLAR RATIO WITH $Pd(PPh_3)_4$ (0.04 mol/mol of bromostyrene) AND POTASSIUM ACETATE (1 mol) IN ANISOLE (closed vessel under N_2) FOR 24 h

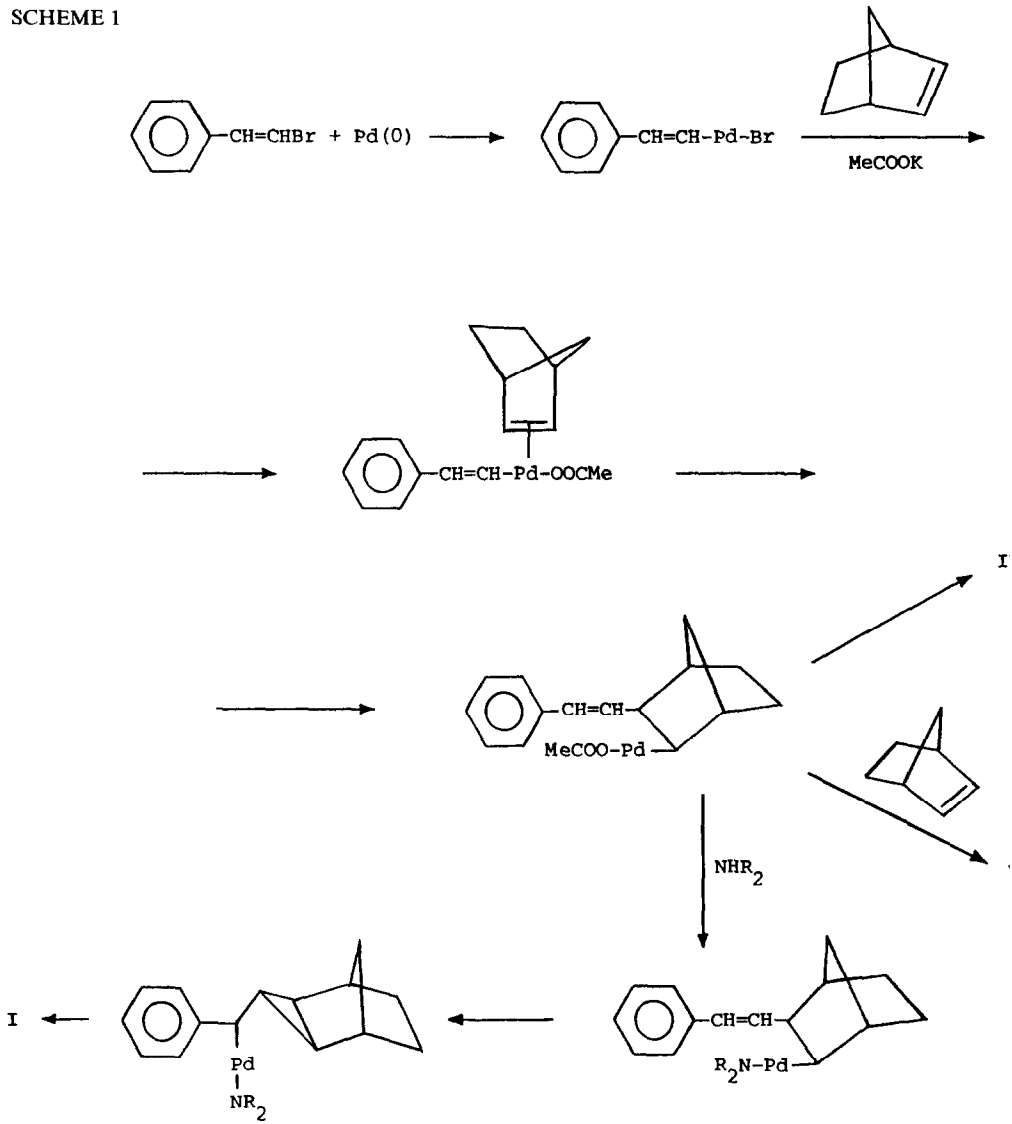
R in HNR_2	*T* (°C)	I	IV	V
$(CH_2)_4$	80	76	3	6
$(CH_2)_4$	20	12 [a]		
$(CH_2)_5$	105	53	20	8
$(CH_2)_2O(CH_2)_2$	105	42	21	9
Me	105	26	35	16

[a] Quinoline as solvent; 85% of bromostyrene was recovered.

derived from cyclopentane ring closure and H elimination after bicycloheptene insertion [3].

With quinoline as solvent the reaction takes place even at room temperature, although with low conversions. We expected the amine to attack the Pd–C bond before cyclopropane ring closure, but no significant amount of the corresponding compound was obtained. This is rather curious in view of the fact that when a hydride source is used in the absence of amines the reaction can be stopped after the first bicycloheptene insertion [2]. Apparently the amine has a weaker tendency to couple at this stage with the Pd-bonded carbon. This may be due to the fact that the cyclopropane ring closure is a faster process or is accelerated in the presence of the amine. The latter seems to act as a ligand by preventing in part the insertion of a

SCHEME 1



second bicycloheptene molecule and the subsequent ring closure on the styryl double bond to give V [3]. This reaction becomes more important if the amine/Pd ratio is decreased below 2 mol/mol. The type of amine plays a major role, the basicity and steric hindrance both being very important. If the various amines are arranged in a series according to the yields obtained, the sequence is strikingly similar to that of the heat of reaction between the same amines and Me_3B [4]; thus the order of basicity, based on the equilibrium constant for complexation with Me_3B in the gas phase at 100 °C, is: pyrrolidine 290, piperidine 48, dimethylamine 47, diethylamine 0.82. This has been taken as a clear indication of steric effects, and we believe that the same effects are responsible for the failure of diethylamine to react and for the great difference from dimethylamine (in spite of the fact that volatility of the latter lowers its concentration in the liquid phase, thus leading to lower yields of I).

On the basis of the present and previous observations the process can be depicted as in Scheme 1 (the inert ligands triphenylphosphine and amines are omitted).

An initial oxidative addition reaction leads to styrylpalladium bromide. The latter inserts bicycloheptene stereoselectively (*cis,exo*) under the promoting action of the carboxylato group [1]. Exchange with the amine leads to a palladium amide. Further stereoselective insertion of the remaining double bond gives a new palladium complex from which reductive C–N coupling produces compound I. The by-products IV and V, not involving reaction with the amine, are formed at an earlier stage, by cyclopropane ring formation or by bicycloheptene insertion and cyclopentane ring formation, respectively.

Experimental

All reagents were commercial products; amines were distilled before use. All reactions were carried out under nitrogen. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker CXP 200 and Varian XL 100 spectrometers at 200 and 25.2 MHz, respectively, in $CDCl_3$ with TMS as internal standard. The mass spectra were obtained with a Finnigan 1020 instrument at 70 eV.

General procedure for the synthesis of amines I (3-(1-(N-dialkylamino)benzyl)-tricylo[3.2.1.0^{2,4}]octane)

The desired amine (4–6 mmol) was introduced under nitrogen into a Schlenk-type flask, containing $Pd(PPh_3)_4$ (92 mg, 0.08 mmol), potassium acetate (206 mg, 2.1 mmol), bicycloheptene (200 mg, 2.1 mmol) and *E*-β-bromostyrene (385 mg, 2.1 mmol) in anisole (2 ml). The mixture was stirred at 80–105 °C for 24 h. Compound I was obtained by acid–base extraction. After conventional treatment of the remaining organic solution, compounds IV and V were obtained as a mixture by chromatography on a SiO_2 column, using hexane as eluent. The yields of IV and V were determined by GLC.

Hydrogenolysis of I (R = $(CH_2)_5$)

Compound I (R = $(CH_2)_5$) (300 mg, 1.1 mmol) was dissolved in ethyl acetate (20 ml) and the mixture was hydrogenated on Pd/C at 50 °C for 4 h with stirring. After acid–base extraction of the filtrate and distillation of the solvent, which contained piperidine, the unreacted amine I (120 mg, 0.4 mmol) was recovered. The remaining organic phase was dried over Na_2SO_4 and evaporation of the solvent under reduced

pressure gave compound II (101 mg, 0.5 mmol) along with small amount of III. III was identical with the hydrogenation product from 2-styrylbicycloheptane [2].

Characterization of the products

I (R = $(CH_2)_4$). MS: M^+ 267, *m/e* 196, 190, 168, 167, 160, 153, 141, 130, 129, 128, 117, 115, 105, 104, 92, 91, 79, 78, 77, 70, 67, 65, 55, 54, 53, 51; ^{1}H NMR: δ 7.36–7.17 (m, 5H, aromatic protons), 2.75–2.55 (m, 2H, 2HC–N), 2.46–2.28 (m, 3H, 2HC–N, HC(1) or HC(5)), 2.18(d, *J* 10 Hz, 1H, HC–Ph), 2.08–2.02 (m, 1H, HC(1) or HC(5)), 1.84–1.67 (m, 4H, C–$(CH_2)_2$–C), 1.49–1.10 (m, 5H, HC(3), H_2C(6), H_2C(7)), 0.99 (br d, *J* 10 Hz, 1H, HC(8) *syn*), 0.84 (br d, *J* 7 Hz, 1H, HC(2) or HC(4)), 0.58 (br d, *J* 10 Hz, 1H, HC(8) *anti*), 0.41 (br d, *J* 7 Hz, 1H, HC(2) or HC(4)) ppm; ^{13}C NMR: δ 144.0, 127.8, 127.3, 126.5 (aromatic carbons), 73.5 (d, CHPh), 53.3 (t, $2CH_2$–N), 35.8, 35.5 (d, C(1), C(5)), 29.4 (t, C(6) and C(7)), 28.6 (t, C(8)), 25.7 (d, C(3)), 23.1 (t, C–$(CH_2)_2$–C), 20.7, 20.3 (d, C(2), C(4)) ppm.

I (R = $(CH_2)_5$). MS: M^+ 281, *m/e* 204, 196, 174, 168, 167, 153, 141, 130, 129, 128, 117, 115, 105, 91, 84, 79, 77, 67, 65, 57, 56, 55, 54, 53, 51; ^{1}H NMR: δ 7.32–7.15 (m, 5H, aromatic protons), 2.68–2.49 (m, 2H, 2HC–N), 2.35–2.23 (m, 3H, 2HC–N, HC(1) or HC(5)), 2.20 (d, *J* 10 Hz, HC–Ph), 2.10–2.01 (m, 1H, HC(1) or HC(5)), 1.60–1.05 (m, 10H, H_2C(6), H_2C(5), $3CH_2$ groups of the piperidino ring), 1.04–0.90 (m, 2H, HC(3), HC(8) *syn*), 0.80 (br d, *J* 7 Hz, HC(2) or HC(4)), 0.58 (br d, *J* 10 Hz, HC(8) *anti*), 0.36 (br d, *J* 7 Hz, HC(2) or HC(4)) ppm; ^{13}C NMR: δ 143.9, 127.7, 126.2 (aromatic carbons), 73.8 (d, CHPh), 52.7 (t, $2CH_2$N), 35.8, 35.5 (d, C(1), C(5)), 29.4 (t, C(6) and C(7)), 28.6 (t, C(8)), 26 .3 (t, $2CH_2$ of the piperidino ring and C(3)), 24.8 (t, CH_2 of the piperidino ring), 20.8, 18.4 (d, C(2), C(4)) ppm.

I (R = $(CH_2)_2O(CH_2)_2$). MS: M^+ 283, *m/e* 206, 197, 189, 176, 141, 131, 130, 129, 128, 117, 115, 105, 91, 79, 77, 67, 65, 57, 56, 55, 54, 51, 42, 41; ^{1}H NMR: δ 7.35–7.10 (m, 5H, aromatic protons), 3.76–3.55 (m, 4H, $O(CH_2)_2$), 2.75–2.56 (m, 2H, 2HC–N), 2.39–2.23 (m, 3H, 2HC–N, HC(1) or HC(5)), 2.19 (d, *J* 10 Hz, HC–Ph), 2.11–2.01 (m, 1H, HC(1) or HC(5)), 1.45–1.10 (m, 4H, H_2C(6), H_2C(7)), 1.00–0.86 (m, 2H, HC(3), HC(8) *syn*), 0.80 (br d, *J* 7 Hz, HC(2) or HC(4)), 0.59 (br d, *J* 10 Hz, HC(8) *anti*), 0.41 (br d, *J* 7Hz, HC(2) or HC(4)) ppm; ^{13}C NMR: δ 142.9, 127.8, 127.6, 126.6 (aromatic carbons), 73.6 (d, CHPh), 67.0 (t, $2CH_2O$), 52.2 (t, $2CH_2N$), 35.7, 35.5 (d, C(1), C(5)), 29.3 (t, C(6) and C(7)), 28.5 (t, C(8)), 26.3 (d, C(3)), 20.4, 18.4 (d, C(2), C(4)) ppm.

I (R = Me). MS: M^+ 241, *m/e* 197, 168, 167, 164, 153, 147, 146, 141, 134, 129, 128, 118, 117, 115, 105, 91, 79, 77, 67, 65, 51; ^{1}H NMR: δ 7.38–7.12 (m, 5H, aromatic protons), 2.39–2.32 (m, 1H, HC(1) or HC(5)), 2.27 (s, 6H, $2CH_3$), 2.17 (d, *J* 9 Hz, HC–Ph), 2.13–2.06 (m, 1H, HC(1) or HC(5)), 1.49–1.15 (m, 4H, H_2C(6), H_2C(5)), 1.09 (dt, *J* 9 Hz, *J* 3Hz, 1H, HC(3)), 1.02 (br d, *J* 10 Hz, 1H, HC(8) syn), 0.85 (br d, *J* 7 Hz, 1H, HC(2) or HC(4)), 0.63 (br d, *J* 10 Hz, 1H, HC(8) *anti*), 0.40 (br d, *J* 7 Hz, 1H, HC(2) or HC(4)) ppm; ^{13}C NMR: δ 143.2, 127.8, 127.6, 126.5 (aromatic carbons), 74.3 (d, CHPh), 43.9 (q, $N(CH_3)_2$), 35.8, 35.6 (d, C(1), C(5)), 29.4 (t, C(6) and C(7)), 28.6 (t, C(8)), 26.4 (d, C(3)), 20.8, 18.9 (d, C(2), C(4)) ppm.

IV. MS: M^+ 196, *m/e* 168, 167, 166, 165, 155, 153, 152, 142, 141, 130, 129, 128, 127, 115, 102, 91, 77, 67, 65, 63, 51, 41; the ^{1}H NMR spectrum of the mixture of IV and V shows at δ 6.63 ppm a characteristic singlet of =CH–Ph grouping. Hydrogenolysis of IV (2/1 mixture with V) carried out in ethyl acetate on Pd/C at room temperature, gave compound III, almost quantitatively, together with the hydrogenation product of V.

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