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Synthesis of Pyrrolidine Derivatives by the Palladium-Catalyzed Cyclization of *N*-(2-Cyclohexenyl)bromoacetamide Derivatives

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N-(2-Cyclohexenyl)bromoacetamide derivatives underwent intramolecular cyclization to give pyrrolidine derivatives in the presence of a base and a catalytic amount of palladium catalyst.

INTRODUCTION

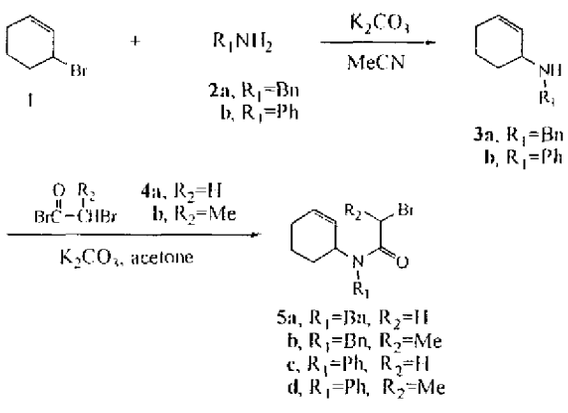
Pyrrolidines bearing bicyclic skeletons are components of various alkaloids[1] or amino acid derivatives with potent physiological activities.[2] The efficient construction of the pyrrolidine ring is important to their syntheses. Most approaches to pyrrolidine involve acyl-nitrogen bond formation,[3] but the apparently equally useful mode of carbon-carbon bond formation has received little attention. Recently, it has become very popular to use organometallic reagents in the synthesis of heterocyclic ring systems;[4] the extensive studies of palladium catalysis in particular have uncovered many new processes for organic synthesis.[5] In the alkylation of olefins *via* σ-alkylpalladium(II) complexes, reactions have been limited to methyl, allyl, and benzyl halides.[6] The report that α-halocarbonylated compounds afford fairly stable σ-alkylmetal complexes[7] with low-valent metal complexes[8] prompted us to extend this reaction by intramolecular cyclization of *N*-(2-cyclohexenyl)bromoacetamide derivatives *via* alkylpalladium intermediate.

RESULTS AND DISCUSSION

The required *N*-(2-cyclohexenyl)bromoacetamide derivatives **5** were prepared by bromoacetylation of allylic amines. Thus, 3-bromocyclohexene (**1**) was reacted with amines **2** in the presence of K_2CO_3 to give 2-cyclohexenylamines **3**, which were treated with bromoacetyl bromides **4** to produce *N*-(2-cyclohexenyl)bromoacetamide derivatives **5** (Scheme I).

When *N*-benzyl-*N*-(2-cyclohexenyl)bromoacetamide (**5a**) (1 mmol) was allowed to react with 10 mol% 1:2 $Pd(OAc)_2$-PPh_3 in refluxing MeCN in the presence of NEt_3 for 2 h, the direct introduction of the olefin group into the bromoacetamide system led to cyclization to afford the product of **6a** in 21% yield (entry 1 in Table 1). In order to increase the yield of the cyclized product and to investigate

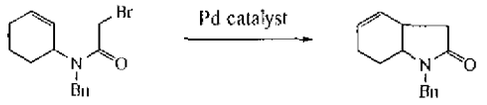
Scheme I



the reaction mechanism, this reaction was examined under various reaction conditions. As indicated in Table 1, the bidentate ligand 1,4-bis(diphenylphosphino)butane (dppb) increased the yield of the cyclized product significantly (entries 9 and 10). One possible explanation for this observation is that suitable phosphine ligands help to maximize the concentration of the active catalyst by preventing the loss of palladium metal. It is well-known that, in catalytic processes using a palladium compound as catalyst precursor, loss of the palladium catalyst due to deposition of palladium metal is a distinct possibility.[9] To regenerate the palladium(0) catalyst, an amine base such as NEt_3, K_2CO_3 or proton sponge [1,8-bis(dimethylamino)naphthalene] was required. Three useful solvents are MeCN, HMPA or DMF; MeCN gave the best results (entries 1-3). Among palladium catalysts including $Pd(OCOCF_3)_2$ (entries 7 and 10), $Pd(PPh_3)_4$ (entry 8), $PdCl_2$ (entry 11), and $PdCl_2$-PPh_3 (entry 6), $Pd(OAc)_2$ was found to be superior (entry 9).

Table 2 summarizes the results for the reaction of **5b-c** with a palladium catalyst. Treatment of **5b** with $Pd(OAc)_2$-dppb gave the cyclized products **6b** and **7a** in the yield of 40% and 8%, respectively (entry 1 in Table 2). An examination of the ^1H NMR spectrum of **6b** thus obtained indicated the presence of a mixture of two diastereomers in a ratio of

Table 1. Pd-catalyzed Cyclization of *N*-Benzyl-*N*-(2-cyclohexenyl)bromoacetamide (**5a**)



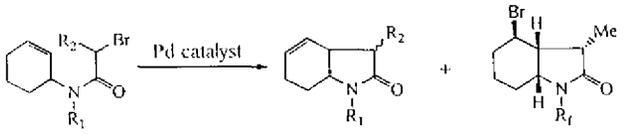
5a 6a

Entry	Catalyst	(mol eq.)	Base	Solvent[a]	Yield of **6a**[b]
1	$Pd(OAc)_2$ -PPh_3	(0.10) (0.20)	NEt_3	MeCN	21%
2	$Pd(OAc)_2$ -PPh_3	(0.10) (0.20)	NEt_3	HMPA	17
3	$Pd(OAc)_2$ -PPh_3	(0.10) (0.20)	NEt_3	DMF	12
4	$Pd(OAc)_2$ -PPh_3	(0.10) (0.20)	Proton sponge	MeCN	14
5	$Pd(OAc)_2$ -PPh_3	(0.10) (0.20)	K_2CO_3	MeCN	10
6	$PdCl_2$ -PPh_3	(0.10) (0.20)	NEt_3	MeCN	13
7	$Pd(OCOCF_3)_2$ -PPh_3	(0.10) (0.20)	NEt_3	MeCN	13
8	$Pd(PPh_3)_4$	(0.10)	NEt_3	MeCN	10
9	$Pd(OAc)_2$ -dppb	(0.10) (0.20)	NEt_3	MeCN	55
10	$Pd(OCOCF_3)_2$ -dppb	(0.10) (0.20)	NEt_3	MeCN	39
11	$PdCl_2$	(0.10)	NEt_3	MeCN	17

[a] in MeCN was refluxed for 2 h; in HMPA or DMF was stirred at 65 °C for 6 h. [b] Isolated yield.

1:1. The structure of **7a** was determined by its 2D-NMR spectra (C, H-COSY) and NOE experiments. This palladium-catalyzed cyclization presumably proceeds by oxidative addition of the bromoacetyl group to palladium(0) species, followed by insertion of the double bond into the σ-alkylpalladium bond and the loss of a palladium hydride species by β-elimination to afford compound **6b**. The palladium hydride species is attacked by the base to regenerate the palladium(0) catalyst. Compound **7a** was considered to be a reductive elimination product from **9** and no β-elimination of the intermediate **8** to compound **10** was observed. Steric repulsion between a methyl group and a large palladium bromide group may selectively afford **7a** and contribute to the formation of the dehydrohalogenation product **6b** (Scheme II). By changing the catalyst to $Pd(OCOCF_3)_2$-dppb, the reaction afforded only compound **6b** (entry 2). In the presence of $PdCl_2$-dppb, the products **6b** and **7a** were obtained in the yield of 16% and 5%, respectively (entry 3). Compound **5c** was treated with $Pd(OAc)_2$-dppb to give the sole cyclized product **6c** in the yield of 43% (entry 4). Treatment of **5d** with $Pd(OAc)_2$-dppb gave the cyclized

Table 2. Pd-catalyzed Cyclization of **5b-d**



5 b, R_1=Bn, R_2=Me
c, R_1=Ph, R_2=H
d, R_1=Ph, R_2=Me

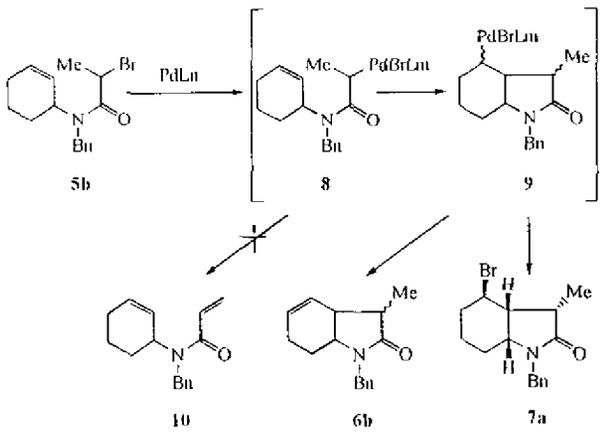
6 b, R_1=Bn, R_2=Me
c, R_1=Ph, R_2=H
d, R_1=Ph, R_2=Me

7a, R_1=Bn
b, R_1=Ph

Entry	5[a]	Catalyst	(mol eq.)	Product 6	Product 7	Yield[b] (%)	Ratio 6:7
1	**5b**	$Pd(OAc)_2$ -dppb	(0.10) (0.20)	**6b**	**7a**	48	5:1
2	**5b**	$Pd(OCOCF_3)_2$ -dppb	(0.10) (0.20)	**6b**		29	1:0
3	**5b**	$PdCl_2$ -dppb	(0.10) (0.20)	**6b**	**7a**	21	3:1
4	**5c**	$Pd(OAc)_2$ -dppb	(0.10) (0.20)	**6c**		43	1:0
5	**5d**	$Pd(OAc)_2$ -dppb	(0.10) (0.20)	**6d**	**7b**	77	1:5

[a] in the presence of NEt_3 and MeCN, and was refluxed for 2 h. [b] Isolated yield.

Scheme II



products **6d** as a mixture of two diastereomers in a ratio of 1:1 and **7b** in fairly good yields (entry 5).

These results suggest that σ-alkylpalladium complexes, formed from α-bromoacetamide derivatives, may be useful intermediates in organic synthesis.

EXPERIMENTAL SECTION

IR absorption spectra were recorded on a Shimadzu IR-27G spectrophotometer. Proton NMR was measured with a Varian Gemini-200 spectrometer. Chemical shifts (δ)

and coupling constants (Hz) were measured with respect to TMS. MS and high resolution mass spectra (HRMS) were taken on a Hewlett Packard 5989A or JEOL JMS D-100 instrument, with a direct inlet system.

N-Benzyl-N-(2-cyclohexenyl)amine (3a)

To a solution of benzylamine (**2a**) (3.19 g, 30 mmol) and K_2CO_3 (10.28 g, 74.3 mmol) in MeCN (20 mL) was added a solution of 3-bromocyclohexene (**1**) (4 g, 24.8 mmol) in MeCN (10 mL) under ice-cooling. The reaction mixture was then stirred at room temperature overnight. Solvent was removed under reduced pressure and column chromatography (4:1 *n*-hexane/ethyl acetate) of the residue afforded **3a** (3.85 g, 83%). IR ($CHCl_3$) ν 3325 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (bs, 1H, NH), 1.47-2.01 (m, 6H), 3.13-3.26 (m, 1H, NCH), 3.82 (bs, 2H, NCH_2), 5.70-5.78 (m, 2H, vinyl), 7.21-7.36 (m, 5H, ArH); EI-MS *m/z* 187 (M^+). HRMS Calcd for $C_{13}H_{17}N$ 187.1361. Found 187.1360.

N-Phenyl-N-(2-cyclohexenyl)amine (3b)

As described for **3a**, reaction of aniline (**2b**) (2.77 g, 30 mmol) with 3-bromocyclohexene (**1**) (4 g, 24.8 mmol) in the presence of K_2CO_3 (10.28 g, 74.3 mmol) afforded **3b** (3.43 g, 80%). IR ($CHCl_3$) ν 3340 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57-2.06 (m, 6H), 3.49 (bs, 1H, NH), 3.98 (bs, 1H, NCH), 5.70-5.90 (m, 2H, vinyl), 6.58-6.72 (m, 3H, ArH), 7.11-7.23 (m, 2H, ArH); EI-MS *m/z* 173 (M^+). HRMS Calcd for $C_{12}H_{15}N$ 173.1204. Found 173.1205.

N-Benzyl-N-(2-cyclohexenyl)bromoacetamide (5a)

A solution of *N*-benzyl-*N*-(2-cyclohexenyl)amine (**3a**) (2 g, 10.7 mmol) and K_2CO_3 (2.95 g, 21.4 mmol) in acetone (20 mL) was added a solution of bromoacetyl bromide (**4a**) (2.59 g, 12.8 mmol) in ether (10 mL) under ice-cooling. The reaction mixture was then stirred at room temperature for 5 h. Solvent was removed under reduced pressure and column chromatography (4:1 *n*-hexane/ethyl acetate) of the residue afforded **5a** (1.81 g, 55%). IR ($CHCl_3$) ν 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25-2.23 (m, 6H), 3.65, 3.99 (s and s, 2H, $COCH_2$), 4.30-4.72 (m, 3H, NCH_2Ph and NCH), 5.43-5.53 (m, 1H, vinyl), 5.85-5.96 (m, 1H, vinyl), 7.18-7.40 (m, 5H, ArH); EI-MS *m/z* 309 (M^++2), 307 (M^+), 228 (M^+-Br). HRMS Calcd for $C_{15}H_{18}{}^{79}BrNO$ 307.0572. Found 307.0571.

N-Benzyl-N-(2-cyclohexenyl)-2-bromopropionamide (5b)

As described for **5a**, reaction of *N*-benzyl-*N*-(2-cyclohexenyl)amine (**3a**) (2 g, 10.7 mmol) with 2-bromopropionyl bromide (**4b**) (2.77 g, 12.8 mmol) in the presence of K_2CO_3 (2.95 g, 21.4 mmol) afforded **5b** (1.55 g, 45%). IR ($CHCl_3$) ν 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22-2.05 (m, 6H), 1.69, 1.71 (d and d, J = 6.5 Hz, 3H, CH_3), 4.11-4.25 (m, 1H, CHBr), 4.40-4.88 (m, 3H, NCH_2Ph and NCH), 5.43-5.94 (m, 2H, vinyl), 7.14-7.41 (m, 5H, ArH); EI-MS *m/z* 323 (M^++2), 321 (M^+), 242 (M^+-Br). HRMS Calcd for $C_{16}H_{20}{}^{79}BrNO$ 321.0728. Found 321.0728.

N-(2-Cyclohexenyl)-N-phenylbromoacetamide (5c)

As described for **5a**, reaction of *N*-phenyl-*N*-(2-cyclohexenyl)amine (**3b**) (2 g, 11.5 mmol) with bromoacetyl bromide (**4a**) (2.8 g, 13.9 mmol) in the presence of K_2CO_3 (3.19 g, 23.1 mmol) afforded **5c** (2.04 g, 60%). IR ($CHCl_3$) ν 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26-1.96 (m, 6H), 3.57 (s, 2H, CH_2Br), 5.35-5.43 (m, 1H, NCH), 5.59-5.64 (m, 1H, vinyl), 5.74-5.80 (m, 1H, vinyl), 7.19-7.45 (m, 5H, ArH); EI-MS *m/z* 295 (M^++2), 293 (M^+), 214 (M^+-Br). HRMS Calcd for $C_{14}H_{16}{}^{79}BrNO$ 293.0415. Found 293.0416.

N-(2-Cyclohexenyl)-N-phenyl-2-bromopropionamide (5d)

As described for **5a**, reaction of *N*-phenyl-*N*-(2-cyclohexenyl)amine (**3b**) (2 g, 11.5 mmol) with 2-bromopropionyl bromide (**4b**) (2.99 g, 13.9 mmol) in the presence of K_2CO_3 (3.19 g, 23.1 mmol) afforded **5d** (1.92 g, 54%). IR ($CHCl_3$) ν 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26-1.91 (m, 6H), 1.72 (d, J = 6.8 Hz, 3H, CH_3), 4.10 (q, J = 6.8 Hz, 1H, $C\underline{H}CH_3$), 5.36-5.41 (m, 1H, NCH), 5.65-5.69 (m, 1H, vinyl), 5.74-5.79 (m, 1H, vinyl), 7.07-7.42 (m, 5H, ArH); EI-MS *m/z* 309 (M^++2), 307 (M^+), 228 (M^+-Br). HRMS Calcd for $C_{15}H_{18}{}^{79}BrNO$ 307.0572. Found 307.0573.

Cyclization of N-benzyl-N-(2-cyclohexenyl)bromoacetamide (5a) with $Pd(OAc)_2$

A mixture of **5a** (308 mg, 1 mmol), $Pd(OAc)_2$ (22 mg, 0.1 mmol), dppb (85 mg, 0.2 mmol), and NEt_3 (202 mg, 2 mmol) in MeCN (10 mL) was refluxed for 2 h. Solvent was removed under reduced pressure and column chromatography (2:1 *n*-hexane/ethyl acetate) of the residue afforded *N*-benzyl-4-indolin-2-one (**6a**) (125 mg, 55%). IR ($CHCl_3$) ν 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50-2.29 (m, 4H), 2.57-2.82 (m, 3H), 3.52-3.62 (m, 1H, NCH), 3.98 (d, J = 15.0 Hz, 1H, NC$\underline{H}$Ph), 5.02 (d, J = 15.0 Hz, 1H, NC$\underline{H}$Ph), 5.28-5.95 (m, 2H, vinyl), 7.24-7.32 (m, 5H, ArH), EI-MS *m/z* 227 (M^+). HRMS Calcd for $C_{15}H_{17}NO$ 227.1310. Found 227.1310.

Cyclization of N-benzyl-N-(2-cyclohexenyl)-2-bromopropionamide (5b) with $Pd(OAc)_2$

As described for **5a**, reaction of **5b** (322 mg, 1 mmol), $Pd(OAc)_2$ (22 mg, 0.1 mmol), dppb (85 mg, 0.2 mmol), and NEt_3 (202 mg, 2 mmol) in MeCN (10 mL) afforded *N*-benzyl-3-methyl-4-indolin-2-one (**6b**) (96 mg, 40%) as an iso-

meric mixture (1:1, *determined by* ^{1}H NMR *spectroscopy*) and *N*-benzyl-4-bromo-3-methyl-2-oxo-perhydroindole (**7a**) (26 mg, 8%). **6b**: IR ($CHCl_3$) ν 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.19 and 1.28 (d, both J = 6.8 Hz, total 3H, CH_3), 1.35-2.10 (m, 4H), 2.27-2.70 (m, 2H, C<u>H</u>C<u>H</u>CH_3), 3.36-3.65 (m, 1H, NCH), 3.96 and 4.05 (d, both J = 15.2 Hz, total 1H, NC<u>H</u>Ph), 4.96 and 4.98 (d, both J = 15.0 Hz, total 1H, NC<u>H</u>Ph), 5.71-5.76 (m, 2H, vinyl), 7.18-7.37 (m, 5H, ArH); EI-MS *m/z* 241 (M^+). HRMS Calcd for $C_{16}H_{19}NO$ 241.1467. Found 241.1466. **7a**: IR ($CHCl_3$) ν 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (d, J = 7.1 Hz, 3H, CH_3), 1.33-2.04 (m, 6H), 2.24-2.33 (m, 1H, C<u>H</u>CHCH$_3$), 2.49 (quin, J = 7.2 Hz, 1H, C<u>H</u>CH$_3$), 3.56-3.65 (m, 1H, NCH), 4.01 (d, J = 15.0 Hz, 1H, NC<u>H</u>Ph), 4.25-4.33 (m, 1H, CHBr), 4.90 (d, J = 15.0 Hz, 1H, NC<u>H</u>Ph), 7.23-7.34 (m, 5H, ArH); EI-MS *m/z* 323 (M^++2), 321 (M^+), 242 (M^+-Br). HRMS Calcd for $C_{16}H_{20}{}^{79}BrNO$ 321.0728. Found 321.0727.

Cyclization of *N*-(2-cyclohexenyl)-*N*-phenylbromoacetamide (5c) with Pd(OAc)$_2$

As described for **5a**, reaction of **5c** (294 mg, 1 mmol), $Pd(OAc)_2$ (22 mg, 0.1 mmol), dppb (85 mg, 0.2 mmol), and NEt_3 (202 mg, 2 mmol) in MeCN (10 mL) afforded *N*-phenyl-4-indolin-2-one (**6c**) (92 mg, 43%). IR ($CHCl_3$) ν 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.72-2.15 (m, 4H), 2.67-2.75 (m, 2H, $COCH_2$), 2.96-3.08 (m, 1H, C<u>H</u>CH=CH), 4.33-4.42 (m, 1H, NCH), 5.59-5.92 (m, 2H, vinyl), 7.14-7.41 (m, 5H, ArH); EI-MS *m/z* 213 (M^+). HRMS Calcd for $C_{14}H_{15}NO$ 213.1154. Found 213.1153.

Cyclization of *N*-(2-cyclohexenyl)-*N*-phenyl-2-bromopropionamide (5d) with Pd(OAc)$_2$

As described for **5a**, reaction of **5d** (308 mg, 1 mmol), $Pd(OAc)_2$ (22 mg, 0.1 mmol), dppb (85 mg, 0.2 mmol), and NEt_3 (202 mg, 2 mmol) in MeCN (10 mL) afforded *N*-phenyl-3-methyl-4-indolin-2-one (**6d**) (30 mg, 13%) as an isomeric mixture (1:1, determined by ^{1}H NMR spectroscopy) and *N*-phenyl-4-bromo-3-methyl-2-oxo-perhydroindole (**7b**) (199 mg, 64%). **6d**: mp 124-126 °C. IR ($CHCl_3$) ν 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23 and 1.32 (d, both J = 6.8 Hz, total 3H, CH_3), 1.53-2.11 (m, 4H), 2.45-2.60 (m, 2H, C<u>H</u>C<u>H</u>CH$_3$), 4.01-4.29 (m, 1H, NCH), 5.74-5.87 (m, 2H, vinyl), 7.26-7.58 (m, 5H, ArH); EI-MS *m/z* 227 (M^+). HRMS Calcd for $C_{15}H_{17}NO$ 227.1310. Found 227.1309. **7b**: IR ($CHCl_3$) ν 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (d, J = 6.6 Hz, 3H, CH_3), 1.49-1.97 (m, 6H), 2.51-2.59 (m, 2H, C<u>H</u>C<u>H</u>CH$_3$), 4.31-4.41 (m, 1H, NCH), 4.46-4.52 (m, 1H, CHBr), 7.16-7.50 (m, 5H, ArH); EI-MS *m/z* 309 (M^++2), 307 (M^+), 228 (M^+-Br). HRMS Calcd for $C_{15}H_{18}{}^{79}BrNO$ 307.0572. Found 307.0572.

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Key Words

Palladium-catalyzed cyclization; Pyrrolidine.

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