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# CONCISE SYNTHESIS OF TETRAHYDROPHENANTHRIDONE BY PALLADIUM REAGENT†

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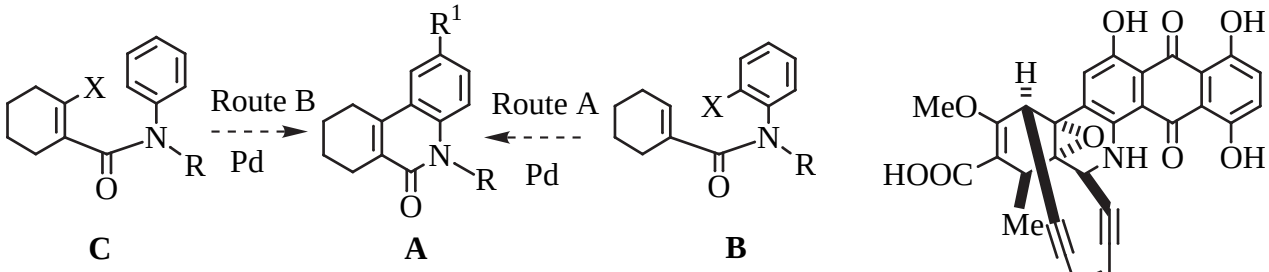
**Abstract**---Heck reaction of *N*-(2-halophenyl)-*N*-methyl-1-cyclohexene-1-carboxamide (**1**) and 2-bromo-*N*-methyl-*N*-phenyl-1-cyclohexene-1-carboxamide (**4**) using a palladium reagent under several reaction conditions was examined. Reaction of **4** using $Pd(OAc)_2$, DPPP, and $Bu_3P$ afforded tetrahydrophenanthridone (**5**) in excellent yield.

Palladium-assisted arylation of alkenes, such as the Heck, Suzuki-Miyaura, and Stille reactions, is a powerful method for the preparation of functionalized aromatics.[1] Recently, we reported that the aryl-aryl coupling reactions using palladium reagents including a novel palladium reagent prepared from $Pd(OAc)_2$, DPPP (1,3-bis(diphenylphosphino)propane), and $Bu_3P$ were very versatile for the synthesis of heteroaromatic compounds.[2, 3] In order to examine an application of the reaction conditions to arylation of alkenes, we designed the synthesis of 7,8,9,10-tetrahydrophenanthridone (**A**), because functionalized phenanthridones (**A**, $R^1$ = OMe) were versatile starting materials for the synthetic studies on dynemicin A.[4] Two routes (Routes A and B) could be accessible for the preparation of compound **A**. (Scheme 1) However, Overman *et al.* have revealed that Heck reaction of compound **B** (R=Me, X=Br or I) with a catalytic amount of $Pd(OAc)_2$, $PPh_3$, and $NEt_3$ in acetonitrile produced not phenanthridone (**A**) but 3-spiro-2-oxoindoles.[5] Thus, we planned to apply other reaction conditions, including our novel method,[3a] and an arylation reaction of compound **C** using Pd reagents. Here we describe the results of these reactions.

Application of our reaction conditions[3] to **B** afforded spiro compounds, as shown in Table 1, similar to Overman's results. However, interestingly, alkene isomerization occurred to a smaller extent. (see runs 3 and 7) Subsequently, Route B was investigated and the results are summarized in Table 2, indicating that a novel palladium reagent[3a] prepared from $Pd(OAc)_2$, DPPP, and $Bu_3P$ was very effective for Heck reaction of compound **C**, which was prepared from bromo acid and aniline *via* *N*-methylation in 49% total yield.

Synthetic studies on tetrahydrophenanthridone possessing a variety of substituents are currently under way.

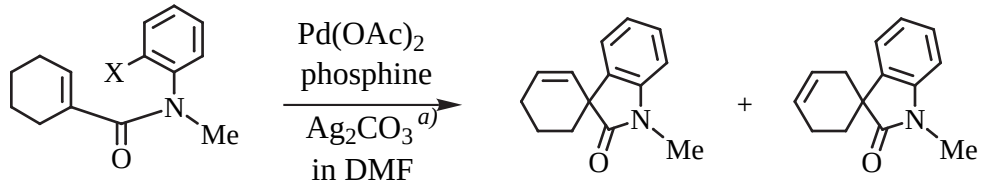
† Dedicated to Professor Yuichi Kanaoka for the celebration of his 75th birthday.




Scheme 1

dynemicin A

**Table 1.** Results of cyclization reactions of *N*-(2-halogenophenyl)-*N*-methyl-1-cyclohexene-1-carboxamides (**1**) to 3-spiro-2-oxoindoles (**2** and **3**).



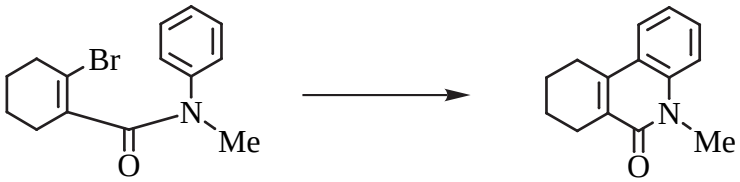

**1a** : X=Br
**1b** : X=I

**2** + **3**

| run | substrate | $Pd(OAc)_2$ (eq.) | phosphine (P/Pd) *b)* | temp. | time | yield (%) (**2**+**3**) | yield (%) **1** | ratio *c)* **2** : **3** |
|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | 0.2 | $PPh_3$ (2) | reflux | 10 h | 43 | 41 | 91: 9 |
| 2 | **1a** | 0.2 | $P(2\text{-tol})_3$ (2) | reflux | 8 h | 93 | 2 | 73:27 |
| 3 | **1a** | 1.0 | *n*-$Bu_3P$ (1), DPPP (1) | reflux | 10 min | 92 | - | 93: 7 |
| 4 *d)* | **1a** | 0.1 | - *e)* | 100˚C | 1 h | 86 | - | 32:68 |
| 5 | **1b** | 0.2 | $PPh_3$ (2) | reflux | 6 h | 90 | 9 | 84:16 |
| 6 | **1b** | 0.2 | $P(2\text{-tol})_3$ (2) | reflux | 20 min | 97 | - | 74:26 |
| 7 | **1b** | 0.2 | *n*-$Bu_3P$ (1), DPPP (1) | reflux | 20 min | 98 | - | 89:11 |

*a)* 2 eq. of $Ag_2CO_3$ was added unless otherwise noted. *b)* Molar ratio between phosphine and Pd. *c)* Determined by HPLC analysis. *d)* 5.5 eq. of AcOK was added as base. *e)* 2 eq. of *n*-$Bu_4NCl$ was added as additive.

**Table 2.** Results of cyclization reactions of 2-bromo-*N*-phenyl-1-cyclohexene-1-carboxamides (**4**) to 7,8,9,10-tetrahydrophenanthridones (**5**). *a)*




**4** **5**

| run | $Pd(OAc)_2$ (eq.) | phosphine (P/Pd) *b)* | base *c)* | time | yield (%) *d)* **5** | yield (%) *d)* **4** |
|---|---|---|---|---|---|---|
| 1 | 1.0 | $PPh_3$ (2) | $Ag_2CO_3$ | 2 h | 33 | 30 |
| 2 | 1.0 | $P(2\text{-tol})_3$ (2) | $Ag_2CO_3$ | 2.5 h | 57 | - |
| 3 | 1.0 | *n*-$Bu_3P$ (1), DPPP (1) | $Ag_2CO_3$ | 10 min | 95 | - |
| 4 | 0.2 | *n*-$Bu_3P$ (1), DPPP (1) | $Ag_2CO_3$ | 8 h | 24 | 64 |

*a)* All reactions were carried out under reflux in DMF. *b)* Molar ratio between phosphine and Pd. *c)* 2 eq. of base was added. *d*) Isolated yield.

## EXPERIMENTAL

Melting points were measured on a micro melting point hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded on a JASCO A-102 or JASCO FT/IR 350 spectrophotometer and $^1$H-NMR spectra in deuteriochloroform on a Hitachi R-1500 (60 MHz) or a Varian VXR-200 (200MHz) or -500 (500 MHz) spectrometer unless otherwise stated. NMR spectral data are reported in parts per million downfield from tetramethylsilane as an internal standard (δ 0.0) and coupling constants are given in Hertz. MS spectra were obtained on a VG-70SE spectrometer. Column chromatography was carried out on silica gel (Wako gel C-200 or Merck, silica gel 60, No. 9385). All experiments were carried out in an argon atmosphere and the extract was washed with brine, dried over anhydrous $MgSO_4$, then filtered, and the filtrate was evaporated to dryness under reduced pressure, unless otherwise noted. $Pd(OAc)_2$ was treated with boiling benzene and the mixture was filtered while hot. The hot filtrate was then concentrated to dryness to give purified $Pd(OAc)_2$.

### General procedure for the preparation of *N*-methylcarboxmides (1) from 1-cyclohexene-1-carboxylic acid and 2-haloaniline

A few drops of dry DMF and oxalyl chloride (1.5 mL, 16.0 mmol) were added to a solution of carboxylic acid (1.0 g, 7.93 mmol) in dry $CH_2Cl_2$ (16 mL) under ice-cooling and the mixture was stirred for 4 h under reflux. Then, the reaction mixture was concentrated to dryness under reduced pressure. To this residue was added a solution of 2-haloaniline (9.5 mmol) in dry $CH_2Cl_2$ (11 mL) and dry $NEt_3$ (1.5 mL, 10.8 mmol) and the whole was stirred for 2 h at 50℃. The reaction mixture was concentrated to dryness and diluted with $CH_2Cl_2$, then washed with 1*N* HCl, aqueous 5% NaOH solution and brine. The residue dissolved in $CHCl_3$ was subjected to column chromatography on silica gel. Elution with hexane : AcOEt (6 : 1) gave NH-carboxamides.

***N*-(2-Bromophenyl)-1-cyclohexene-1-carboxamide :**

Yield : 67%. mp 72.5—73.5℃ (from petr. ether), as colorless needles. IR (KBr) cm$^{-1}$: 3220, 1655, 1630.$^1$H-NMR (60 MHz, $CDCl_3$) δ: 1.55—1.91 (4H, m), 2.10—2.52 (4H, m), 6.80—7.62 (4H, m, Ar-H), 8.00—8.07 (1H, br s, NH), 8.47 (1H, dd, J=8, 2 Hz, Ar-H). *Anal.* Calcd for $C_{13}H_{14}NOBr$: C, 55.73; H, 5.04; N, 5.00. Found: C, 55.72; H, 5.18, N, 4.92.

***N*-(2-Iodophenyl)-1-cyclohexene-1-carboxamide** :

Yield : 57%. mp 68—70℃ (from hexane), as colorless needles. IR (KBr) cm$^{-1}$: 3240, 1655, 1635.$^1$H-NMR (200 MHz, $CDCl_3$) δ: 1.62—1.83 (4H, m), 2.22—2.32 (2H, m), 2.38—2.46 (2H, m), 6.83 (1H, ddd, *J*=7.9, 7.9, 1.5 Hz), 6.89—6.93 (1H, m, $C_2$-H), 7.35 (1H, ddd, *J*=7.9, 7.9, 1.5 Hz, Ar-H), 7.77 (1H, dd, J=7.9, 1.5 Hz, Ar-H), 7.85 (1H, br s, NH), 8.36 (1H, dd, J=7.9, 1.5 Hz, Ar-H). *Anal.* Calcd for $C_{13}H_{14}NOI$: C, 47.73; H, 4.28; N, 5.00. Found: C, 47.92; H, 4.40, N, 4.19.

A suspension of NH-carboxamide (1.79 mmol) and NaH (203 mg, 63% dispersion in mineral oil, 5.35 mmol) in dry DMF (30 mL) was stirred for 30 min at rt and then a solution of methyl iodide (0.11 mL, 1.79 mmol) in dry DMF (20 mL) was added to the reaction mixture. After stirring for 30 min at rt, the reaction mixture was diluted with ether and washed with brine. The residue dissolved in $CHCl_3$ was subjected to

column chromatography on silica gel. Elution with hexane : AcOEt (4 : 1) gave *N*-methylcarboxamides (**1**).

***N*-(2-Bromophenyl)-*N*-methyl-1-cyclohexene-1-carboxamide (1a)**

Yield : 92%. mp 98—100°C (from hexane), as colorless plates. IR (KBr) $cm^{-1}$: 1630. $^1$H-NMR (60 MHz, $CDCl_3$) δ: 1.34—1.54 (4H, m), 1.79—2.16 (4H, m), 3.24 (3H, s, $NCH_3$), 5.85 (1H, m, $C_2$-H), 7.14—7.55 (4H, m, Ar-H). *Anal*. Calcd for $C_{14}H_{16}NOBr$: C, 57.15; H, 5.48; N, 4.76. Found: C, 57.08; H, 5.73, N, 4.69.

***N*-(2-Iodophenyl)-*N*-methyl-1-cyclohexene-1-carboxamide (1b)**

Yield : 91%. mp 95—96.5°C (from hexane), as colorless needles. IR (KBr) $cm^{-1}$: 1625. $^1$H-NMR (60 MHz, $CDCl_3$) δ: 1.45—2.18 (8H, m), 3.23 (3H, s, $NCH_3$), 5.91 (1H, m, $C_2$-H), 6.99—7.96 (4H, m, Ar-H). *Anal*. Calcd for $C_{14}H_{16}NOI$: C, 49.28; H, 4.73; N, 4.11. Found: C, 49.45; H, 4.72, N, 3.97.

**2-Bromo-*N*-methyl-*N*-phenyl-1-cyclohexene-1-carboxamide (4)**

A solution of methyl 2-bromo-1-cyclohexene-1-carboxylate[6] (4.80 g, 21.9 mmol) in MeOH (130 mL) was added to an aqueous 10% NaOH solution (80 mL) and was stirred for 4 h at rt. The reaction mixture was acidified with 1*N* HCl and extracted with AcOEt. The residue was recrystallized from hexane to give 2-bromo-1-cyclohexene-1-carboxylic acid (4.11 g, 92%) mp 102—103.5°C, as colorless needles, (lit.,[7] 103—104°C).

A few drops of dry DMF and oxalyl chloride (0.17 mL, 2.0 mmol) were added to a solution of 2-bromo-1-cyclohexene-1-carboxylic acid (200 mg, 0.98 mmol) in dry $CH_2Cl_2$ (16 mL) under ice-cooling and the mixture was stirred for 4 h under reflux. Then, the reaction mixture was concentrated to dryness under reduced pressure. To this residue was added a solution of aniline (0.20 mL, 2.16 mmol) in dry $CH_2Cl_2$ (2 mL) and dry $NEt_3$ (0.176 mL, 1.23 mmol) and the whole was stirred for 2 h at 40°C. The reaction mixture was concentrated to dryness and diluted with $CH_2Cl_2$, then washed with 10% HCl, aqueous 5% NaOH solution and brine. The residue dissolved in $CHCl_3$ was subjected to column chromatography on silica gel. Elution with hexane : AcOEt (6 : 1) gave 2-bromo-*N*-phenyl-1-cyclohexene-1-carboxamide (204 mg, 75%) as colorless needles, mp 135—137.5°C (from ether). IR (KBr) $cm^{-1}$: 3280, 1660, 1640. $^1$H-NMR (60 MHz, $CDCl_3$) δ: 1.63—1.84 (4H, m), 2.45—2.59 (4H, m), 7.10—7.67 (6H, m, Ar-H and NH). *Anal*. Calcd for $C_{13}H_{14}NOBr$: C, 55.73; H, 5.04; N, 5.00. Found: C, 55.78; H, 5.04, N, 4.89.

A suspension of 2-bromo-*N*-phenyl-1-cyclohexene-1-carboxamide (200 mg, 0.71 mmol) prepared above and NaH (82 mg, 63% dispersion in mineral oil, 2.1 mmol) in dry DMF (14 mL) was stirred for 30 min at rt and then a solution of methyl iodide (0.04 mL, 0.71 mmol) in dry DMF (9 mL) was added to the reaction mixture. After stirring for 30 min at rt, the reaction mixture was diluted with ether and washed with brine. The residue dissolved in ether was subjected to column chromatography on silica gel. Elution with hexane : AcOEt (3 : 1) gave **4** (138 mg, 65%), mp 53.5—55.5°C (from petr. ether) as colorless plates. IR (KBr) $cm^{-1}$: 1630. $^1$H-NMR (60 MHz, $CDCl_3$) δ: 1.37—1.53 (4H, m), 2.06—2.33 (4H, m), 3.35 (3H, s, $NCH_3$),

7.34 (5H, m, Ar-H). *Anal.* Calcd for $C_{14}H_{16}NOBr$: C, 57.15; H, 5.48; N,4.76. Found: C, 57.26; H, 5.41, N, 4.61.

**General procedure for the coupling reaction of *N*-methylanilides (1 or 4) by palladium reagent (see Tables 1 and 2)**

The coupling reaction of *N*-methylanilides (**1** or **4**) (0.24 mmol) in dry DMF (3 mL) was carried out using $Pd(OAc)_2$ and a phosphine ligand in the ratios indicated in Table 2, and 2 mol equivalents of base for the time and at the temperature indicated in Table 2. The reaction mixture was diluted with ether and the precipitates were removed by filtration. The filtrate was washed with brine. The residue was dissolved in AcOEt and subjected to column chromatography on silica gel. Elution with benzene-AcOEt (8 : 1) gave coupling product(s) (a mixture of **2** and **3**, or **4**) and successive elution with the same solvent gave the starting material.

**1'-Methylspiro[2-cyclohexene-1,3-[3*H*]indol]-2'(1'*H*)-one (2)**[5a] **and 1'-methylspiro[3-cyclohexene-1,3-[3*H*]indol]-2'(1'*H*)-one (3)**[5a] **:** the ratio of products (**2** and **3**) was determined by HPLC (column, chemsorb 5Si; eluent, hexane : AcOEt (20 : 1); flow rate, 2.0 mL/min; wave length, 254 nm; $t_R$ for **2** = 19.3 min; $t_R$ for **3** = 16.5 min).

**7,8,9,10-Tetrahydro-5-methylphenanthridin-6(5*H*)-one (5)** : mp 99－101˚C (from hexane) (lit.,[8a] 98－98.5℃, [8b] 100－101°C) as colorless needles. IR (KBr) $cm^{-1}$: 1640. $^1$H-NMR (500 MHz, $CDCl_3$) δ : 1.78－1.89 (4H, m), 2.66－2.69 (2H, m), 2.85－2.88 (2H, m), 3.75 (3H, s, $NCH_3$), 7.24 (1H, ddd, *J*=8.1, 7.0, 1.0 Hz, Ar-H), 7.36 (1H, dd, *J*=8.5, 1.0 Hz, Ar-H), 7.51 (1H, ddd, J=8.5, 7.0, 1.5 Hz, Ar-H), 7.71 (1H, dd, J=8.1, 1.5 Hz, Ar-H). *Anal.* Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.85; H, 7.20, N, 6.54.

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