

Palladium-mediated synthesis of a new eight-membered heterocycle

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Dedicated to Professor Marcial Moreno-Manas on the occasion of his 60th birthday
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Abstract

The eight-membered heterocycle **3** has been prepared in 94% isolated yield starting from phenylnorbornylpalladium chloride dimer, *o*-iodoacetanilide and carbon monoxide in DMF at room temperature. Compound **3** has been unequivocally characterized by X-ray single crystal diffraction. Formation of **3** must involve coordination of the amido group to palladium which prevents ring closure to a hexahydromethanotriphenylene derivative.

Keywords: Palladium catalysis, eight-membered heterocycle, *o*-iodoacetanilide, carbon monoxide

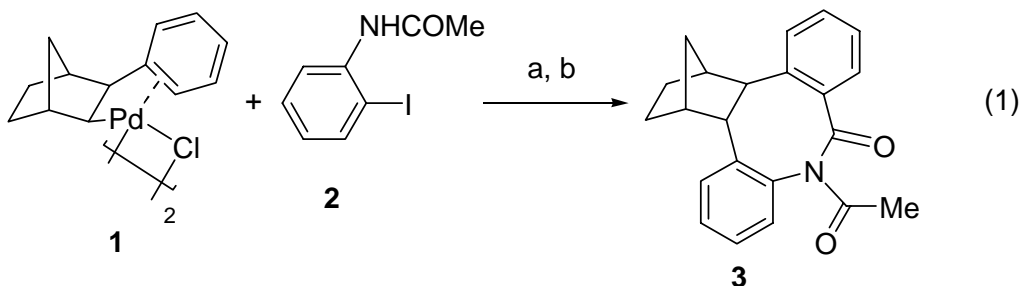
Introduction

The class of azocines,¹ eight-membered cyclic amides, has been little studied. Hypotensive properties have been reported for a class of *N*-substituted[*c,f*]dibenzazocine derivatives.² 6-Methoxytribenzazocine has been prepared by Paquette and coworkers.³ Palladium involving procedures based on different strategies have been recently reported.⁴ As part of our continuing interest in the synthesis of cyclic compounds⁵ as well as in the reactivity of arylnorbornylpalladium complexes,⁶ we have worked out the preparation of a new benzazocine derivative: 5-acetyl-10b,11,12,13,14,14a-hexahydro-11,14-methanotribenz [*b,d,f*]azocin-6-one.

Results and Discussion

Compound **3** was obtained in almost quantitative yield by reaction of phenylnorbornylpalladium chloride dimer⁷ with *o*-iodoacetanilide and carbon monoxide in the presence of K₂CO₃ as a base

and in DMF as solvent. The reaction was run, first under nitrogen for 6 h at room temperature, then under atmospheric pressure of carbon monoxide (Eq. 1). Compound **3** was isolated as a white solid, in 94% yield by flash chromatography. Colourless crystals, suitable for X-ray analysis, were obtained by recrystallization from a solution of hexane–methylene chloride. The crystal structure determination was essential to unequivocally characterise compound **3**, spectroscopic methods alone being insufficient to prove the presence of an eight-membered ring.



(a) 6 h. (b) under CO, 24 h K_2CO_3 , DMF, under N_2 , room temperature

The crystal structure is reported in Figure 1. The norbornyl moiety and the aromatic ring, which are planar within 0.011(6) Å, show normal geometries and their bond distances and angles do not deviate significantly from the expected values. The eight-membered ring is arranged in a boat conformation with four atoms (C1, C6, C14, N16) lying almost in a basal plane and the other four forming the bow (C8, C13) and the stern (C20, C25); consequently the two C8-C13 and C20-C25 aromatic rings are located on the same side with respect to the basal plane and their mean planes form a dihedral angle of 118.7(2)°. In the crystal the molecules are joined by normal van der Waals interactions and the shortest contact is $H10 \cdots O18^i = 2.44(8)$ Å, $i = x, y-1, z$.

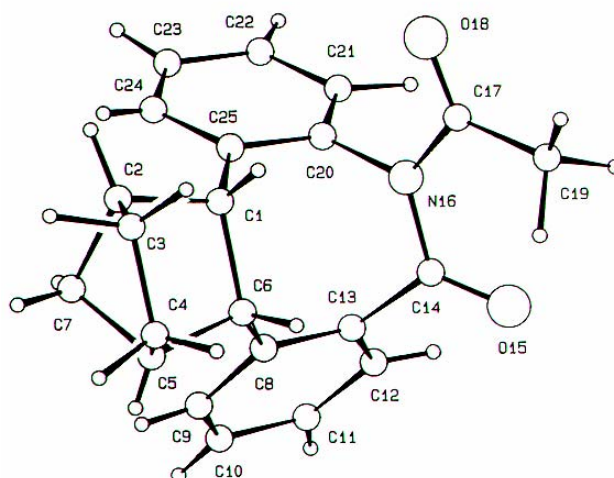
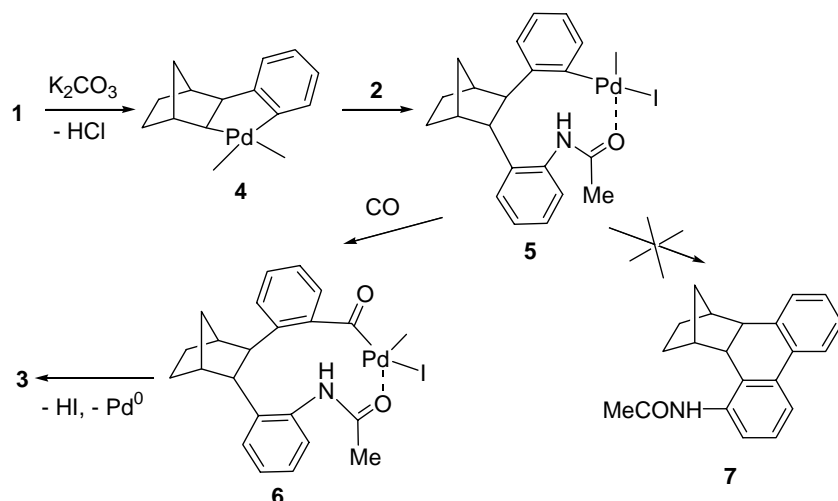


Figure 1. Projection of compound **3** with arbitrary numbering scheme.

The proposed pathway for the formation of the cyclic amide is described in Scheme 1.



Scheme 1. Proposed mechanism for the formation of compound 3.

Formation of the five-membered alkylaromatic palladacycle **4** from complex **1** readily occurs in the presence of a suitable base such as K_2CO_3 in DMF as solvent. The intermediacy of metallacycle **4** has been previously proposed.⁸ The subsequent reaction with *o*-iodoacetanilide leads to complex **5** which is able to insert carbon monoxide giving rise to species **6**. The cyclic amide **3** results from the attack of the NH group to the acylpalladium complex **6**. The reaction of complex **4** with *o*-iodoacetanilide probably involves oxidative addition of the latter to the palladacycle, leading to a palladium(IV) metallacycle which in its turn gives **5** by reductive elimination. Palladium(IV) complexes⁹ resulting from oxidative addition of alkyl halides to alkylaromatic palladacycles have been previously reported by us.¹⁰

The entire process offers a new way to gain access to a rare class of heterocyclic eight-membered rings in high yield through a recently found methodology involving palladacycle formation.⁶ In view of the knowledge of the behaviour of alkylaromatic palladacycles mostly acquired in the authors' laboratory^{6,11} the results now obtained appear rather surprising in that complex **5** does not form a six membered ring, as shown in compound **7**, by coupling the two aryl groups¹¹ and allows carbon monoxide insertion leading to the acylpalladium complex **6**. Therefore we assume coordination of the amido group to account for the behaviour of complex **5**.¹² The reaction is tolerant of *meta* and *para* substituents in both aromatic rings.

The observation that an amido group can successfully interfere with the previously described ring closure,¹¹ has a synthetic potential as well as mechanistic implications.

Thus far a direct attack of the NH group to the arylpalladium bond, which would lead to the formation of a seven-membered ring, could not be obtained even working under conditions of strong basicity and in the presence of chelating ligands, according to procedures described in the literature.¹³ The failure to close this ring, while the eight-membered one was readily formed, is likely due to steric hindrance in the congested transition state.

In conclusion, we have achieved the synthesis of a new benzazocine derivative by taking advantage of the unexpected behaviour of the species **5**, resulting from the reaction of an alkylaromatic palladacycle with an *o*-iodoacetanilide. Further extension of this concept is under study.

Experimental Section

General Procedures. Starting materials were commercial products and were used without further purification. Complex **1** was prepared according to the literature.⁷ DMF was dried over 4 Å molecular sieves and stored under nitrogen. Reactions were carried out under nitrogen using Schlenk techniques. Analytical TLC was performed using silica gel plates (Merck). GLC analyses were run with a Carlo Erba HRGC 5300 instrument equipped with a 30 m long capillary column (SE-30 as the stationary phase). Flash chromatography was carried out with silica gel 60 (ICN Silica 32–63) using hexane-ethyl acetate as eluent. Melting points were determined on an Electrothermal apparatus and are uncorrected. ¹H- and ¹³C-NMR were acquired in CDCl₃ at 20 °C using the solvent as reference on a Bruker AC-300 spectrometer at 300.1 and 75.4 MHz, respectively. Infrared spectra were obtained with a Perkin-Elmer 298 FT-IR spectrophotometer. Mass spectra (*m/z*, relative intensity %) were performed with a Finnigan Mat SSQ 710 instrument working at 70 eV ionisation energy. Elemental analysis was performed using a Carlo Erba EA 1108-Elemental Analyzer.

5-Acetyl-10b,11,12,13,14,14a-Hexahydro-11,14-methanotribenz[*b,d,f*]azocin-6-one (3). Solid K₂CO₃ (14 mg, 0.1 mmol) was introduced under nitrogen into a Schlenk-type flask containing a DMF solution (2mL) of phenylnorbornylpalladium chloride dimer **1**⁷ (31 mg, 0.05 mmol). The resulting mixture was stirred for few minutes until the color changed to light purple. A DMF solution (1 mL) of *o*-iodoacetanilide (26 mg, 0.1 mmol) was added and stirring was continued for 6 hours at room temperature. Nitrogen was replaced by carbon monoxide at atmospheric pressure and the reaction was kept at room temperature under stirring for additional 24 h. The solution was diluted with water (20 mL) and extracted with diethyl ether (3x10 mL). The combined organic phase was dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. The resulting crude was purified by flash chromatography on silica gel using a 7:3 mixture of hexane-ethyl acetate as eluent. Compound **3** (31 mg, 94%) was isolated as a white solid which was recrystallized from hexane to give bright needles of mp 149–151 °C; ¹H-NMR δ 7.15-6.96 (7H, m), 6.90 (1H, d further split, *J* = 7.4 Hz), 3.31 (1H, dd, *J* = 9.8, 1.1 Hz), 3.08 (1H, dd, *J* = 9.8, 1.6 Hz), 2.83 (3H, s), 2.81 (2H, m), 1.89-1.78 (3H, m), 1.56 (1H, d quintets, *J* = 10.0, 1.6 Hz), 1.53-1.45 (2H, m); ¹³C-NMR δ 173.5, 172.6, 140.1, 138.2, 138.0, 137.4, 129.9, 128.9, 128.8, 126.7, 126.1, 126.0, 125.7, 124.8, 50.7, 50.2, 40.0, 39.1, 35.7, 30.2, 29.4, 27.5; IR (KBr) ν 1724, 1638 cm⁻¹; MS (EI, 70 eV): M⁺ 331 (12), *m/z* 288 (100), 264 (40). Anal. calcd. for C₂₂H₂₁NO₂: C, 79.72; H, 6.39; N, 4.23. Found: C, 80.44; H, 6.43; N, 4.26.

X-Ray analysis

The crystal data and pertinent details of the experimental conditions are summarized in Table 1. The Lorentz and polarisation effects were corrected during the data reduction procedure.¹⁴ The structure was solved by direct methods with SIR97¹⁵ and refined by anisotropic full-matrix least-squares with SHELX93.¹⁶ All hydrogen atoms were located in a ΔF map and refined isotropically. Table 2 reports selected bond distances (Å) and bond angles (°).

Table 1. Crystallographic data and experimental information for compound **3**

Formula	C ₂₂ H ₂₁ NO ₂
Formula weight	331.41
Crystal:	
Shape	prism
Dimensions (mm)	0.17 x 0.23 x 0.29
Crystal system	Triclinic
Space group	P-1
Cell Constants:	
a (Å)	9.622(2)
b (Å)	10.547(3)
c (Å)	9.405(3)
α (°)	116.06(4)
β (°)	94.29(3)
γ (°)	80.31(2)
Cell volume (Å ³)	845.18(5)
Formula units	2
F(000)	352
D _{calc} (g cm ⁻³)	1.30
μ _{calc} (cm ⁻¹)	6.19
Cell determination:	
n° of reflections	47
θ range (°)	7.1-33.9
Temperature	room
Diffractometer	Enraf Nonius CAD4
Radiation, wavelength (Å)	CuKα, 1.5418
Standard reflection, step	one, every 100
Decay of standard	none
Reflections measured	3159
Reflections observed [I>2σ(I)]	1828
θ range (°)	3-70
Indices range: h, k, l	-11/11, -12/11, 0/11
No. of refined parameters	311
R (obs. Refl.)	0.048
R (all refl.)	0.080
R _w	0.16
Weights	w=1./[σ ² F _o ² +(0.102P) ²]
Δρ _{min/max}	-0.21/0.21
Source of structure factors	Intern. Tables for X-Ray Crystallography ¹⁸

Table 2. Selected bond distances (Å) and bond angles (°)

C1 - C6	1.589	(9)	C13 - C14	1.507	(12)
C1 - C25	1.505	(8)	C14 - N16	1.407	(9)
C6 - C8	1.518	(7)	N16 - C20	1.452	(8)
C8 - C13	1.401	(10)	C20 - C25	1.390	(10)
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C6 - C1 - C25	113.7	(5)	C14 - N16 - C20	117.8	(5)
C1 - C6 - C8	115.6	(5)	N16 - C20 - C25	120.3	(5)
C6 - C8 - C13	121.3	(6)	C1 - C25 - C20	118.6	(5)
C13 - C14 - N16	114.2	(5)			

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