



## Hydroarylation of 2-azabicyclohept-5-en-3-one

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### ABSTRACT

The hydroarylation of 2-azabicyclo[2.2.1]hept-5-en-3-one with a range of aryl iodides is presented.

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### 1. Introduction

The Pd-catalyzed intermolecular arylation of bicyclic olefins, first demonstrated by Larock, is a powerful method to introduce functionality into bicyclic ring systems.<sup>1</sup> This *exo* selective reaction was later exploited by Regan, where the hydroheteroarylation of a 7-azabicyclo[2.2.1]heptene system afforded a concise synthesis of epibatidine.<sup>1b</sup> This methodology was further extended to epibatidine analogs,<sup>1a,c,d</sup> other biologically active molecules,<sup>2</sup> other bicyclic olefins,<sup>3</sup> and asymmetric variants.<sup>4</sup> In most cases aryl or heteroaryl iodides or diazonium salts<sup>5</sup> and symmetrical olefins are the preferred substrates. A drawback of this methodology is that reductive arylation of unsymmetrical olefins often leads to mixtures of regioisomers.<sup>1f,5,6</sup> More recently, Abe et al. reported that they were not able to effect hydroarylation of a 2-azabicyclo[2.2.1]hept-5-en-3-one system. These authors, instead, turned to a Rh-catalyzed addition of aryl boronic acids to 2-azabicyclo[2.2.1]hept-5-en-3-one (**1**) under microwave irradiation.<sup>6</sup> However, in a previous disclosure of our work on the synthesis of azacyclic insecticides,<sup>7</sup> we demonstrated that **1** is a suitable substrate for the Pd-catalyzed hydroarylation reaction. We disclose herein, our expanded study of the hydroarylation of **1** with a range of aryl iodides including an examination of factors influencing the regioselectivity of the reaction.

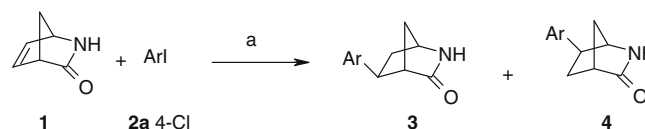
### 2. Results and discussion

The initial reaction between **1** and 1-chloro-4-iodobenzene (**2a**) was conducted with a reaction stoichiometry of 5 mol % Pd-catalyst, 2 equiv of base, 1.4 equiv of formic acid, and 1.1 equiv of the iodoarene (Scheme 1). <sup>1</sup>H NMR analysis of the regioisomeric mixture of *exo* products revealed that the chemical shift of the H<sub>1</sub> proton was particularly diagnostic for identification of each isomer. Thus, the ratio of isomers (5-aryl (**3**):6-aryl (**4**)) could be readily determined by integration of the H<sub>1</sub> proton where **3** (H<sub>1</sub> = 4.04 ppm) and **4** (H<sub>1</sub> = 3.88 ppm).<sup>8</sup>

We briefly examined several reaction parameters to assess their effect on the regioselectivity of the reaction of **1** and **2a**. A survey of bases (Et<sub>3</sub>N, *i*Pr<sub>2</sub>NEt, piperidine) and palladium catalysts prepared from palladium(II) acetate and ligands ranging from bulky, electron-rich phosphines to mono- and bidentate ligands (none, Ph<sub>3</sub>P, (*o*-tolyl)<sub>3</sub>P, *t*Bu<sub>3</sub>P, dppe, dppp, dppb, dppf, ArPhos), revealed no particular influence on the regiochemical preference of the reaction. However, a modest shift in the ratio of regioisomers was noted with change in the solvent.<sup>9</sup> Solvents with lower dielectric constants provided product slightly enriched in **3**, while solvents with higher dielectric constants provided product slightly enriched in **4**.<sup>10</sup> Concentration effects were also briefly considered. Two reactions, using benzene and acetonitrile as solvents, were conducted at a concentration 10-fold more dilute than the standard conditions. The product ratio (**3**:**4**) from the reaction in dilute benzene was shifted toward **3** (entry 2). The product ratio (**3**:**4**) from the reaction in dilute acetonitrile remained unchanged (entry 7 vs entry 6) (Table 1).<sup>11</sup>

The modest selectivity of the hydroarylation reaction between **1** and an aryl iodide led to, at times, an inseparable mixture of 5- and 6-aryl regioisomers. In these cases, N-protection facilitated separation of the regioisomers. Derivatization of the lactam was achieved by employing a stoichiometric quantity of DMAP along with *t*-Boc<sub>2</sub>O and TEA in dichloromethane.<sup>12</sup> The *t*-Boc-protected 5-(4-chlorophenyl) (**5a**) and 6-(4-chlorophenyl) (**6a**) isomers were readily separated on silica gel using 10% ethyl acetate in hexane (Scheme 2). These highly crystalline derivatives allowed for confirmation of the regiochemistry of the hydroarylation by X-ray crystallography.

The ORTEP plot of the X-ray crystal structure of **5a** (Fig. 1) confirmed the regiochemical assignment and the expected *exo* stereochemistry.<sup>13</sup>



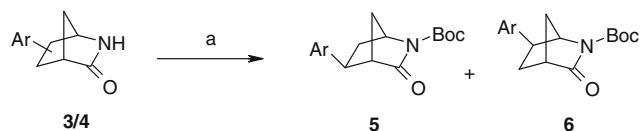
Scheme 1. Reagents: (a) ArI, (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub>, HCO<sub>2</sub>H, base, solvent.

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**Table 1**  
Solvent and concentration effects on the hydroarylation of **1** with **2a**<sup>a</sup>

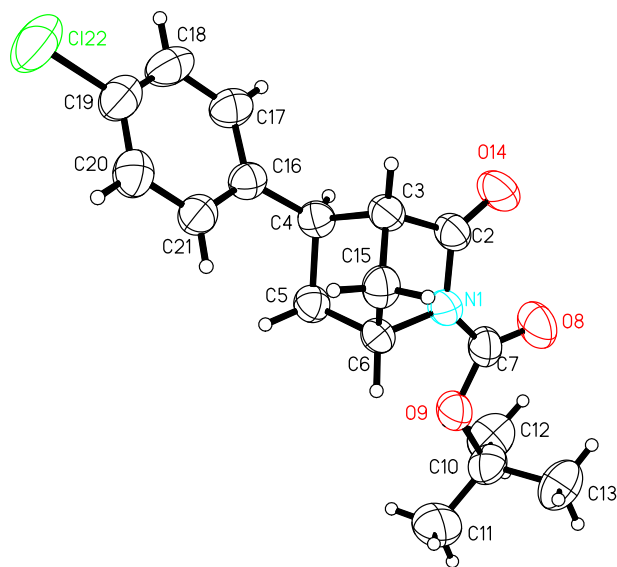
Entry	Solvent/temp	Dielectric constant	Concentration [M, lactam]	Ratio (3:4) <sup>b</sup>	Yield <sup>c</sup>
1	Benzene/70 °C	2.275	0.230	56:44	97
2	Benzene/70 °C		0.023	69:31	98
3	EtOAc/70 °C	6.02	0.230	53:47	94
4	THF/65 °C	7.58	0.230	57:43	100
5	DMF/65 °C	36.71	0.230	38:62	88
6	CH <sub>3</sub> CN/60 °C	37.5	0.230	40:60	85
7	CH <sub>3</sub> CN/60 °C		0.023	39:61	82
8	NMA/65 °C	191.3	0.230	39:61	92

<sup>a</sup> 5 mol % Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, 2 equiv Et<sub>3</sub>N, 1.4 equiv HCO<sub>2</sub>H, 1.1 equiv iodoarene.<sup>b</sup> Based on integration of the H<sub>1</sub> proton.<sup>c</sup> Isolated; after purification by chromatography.**Scheme 2.** Reagents: (a) 1.1 equiv DMAP, Et<sub>3</sub>N, tBOC<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>.

A number of electron rich and electron poor aryl iodides (**2b–g**), as well as a heteroaryl iodide (**2h**), were used in the hydroarylation reaction using the standard conditions to afford mixtures of regioisomeric lactams in good yields (59–98%, Table 2). Aryl bromides could be used (data not shown) but this resulted in lower yields of products and longer reaction times.<sup>14</sup> Aryl triflates failed to provide any products.

### 3. Typical experimental procedures<sup>15</sup>

2-Azabicyclo[2.2.1]hept-5-en-3-one **1** (0.50 g, 4.58 mmol), 1-chloro-4-iodobenzene **2a** (1.20 g, 5.04 mmol) and bis(triphenylphosphine)palladium chloride (0.16 g, 0.23 mmol) were dissolved in 20 mL tetrahydrofuran. Triethylamine (1.3 mL, 9.16 mmol) was added followed by dropwise addition of formic acid (0.25 mL, 6.41 mmol). The reaction mixture was heated under reflux for 16 h, then cooled to room temperature. The reaction was diluted with ethyl acetate and 1 N HCl. The layers were separated and

**Figure 1.** ORTEP plot of **5a**.**Table 2**  
Hydroarylation of **1** with aryl iodides **2**<sup>a</sup>

Entry	Aryl iodide ( <b>2</b> )	Ratio (3:4) <sup>b</sup>	Yield <sup>c</sup>	Time
1	<b>2b</b> Phenyl	56:44	93	16
2	<b>2c</b> 4-Methoxyphenyl	50:50	98	19
3	<b>2d</b> 3,5-Dichlorophenyl	55:45	95	19
4	<b>2e</b> 3-Trifluoromethylphenyl	56:44	91	16
5	<b>2f</b> 4-Methylphenyl	57:43	92	15
6	<b>2g</b> 3-Methoxyphenyl	53:47	98	15
7	<b>2h</b> 6-Chloro-3-pyridinyl	50:50	59	36

<sup>a</sup> 5 mol % Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>, 2 equiv Et<sub>3</sub>N, 1.4 equiv HCO<sub>2</sub>H, 1.1 equiv iodoarene, THF 65 °C.<sup>b</sup> Based on integration of the H<sub>1</sub> proton.<sup>c</sup> Isolated; after purification by chromatography.

the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated. The residue was purified by flash chromatography (silica gel, ethyl acetate) to afford 1.02 g (100%) of **3a:4a** as a 57:43 mixture (NMR) of *exo*-regioisomers. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.35–7.25 (m, 2H), 7.23–7.05 (m, 2H), 5.85 and 5.75 (br s, 1H), 4.04 (s, 0.57H), 3.88 (s, 0.43H), 3.35–3.20 (m, 1H), 2.88–2.82 (overlapping s, 1H), 2.30–2.15 (m, 1H), 2.05–1.95 (m, 2H), 1.80–1.70 (m, 1H). Anal. Calcd for C<sub>12</sub>H<sub>12</sub>NOCl (221.69): C, 65.02; H, 5.46; N, 6.32. Found: C, 64.82; H, 5.40; N, 6.05.

To a solution of 5/6-(4-chlorophenyl)azabicyclo-[2.2.1]heptan-3-ones **3a/4a** (1.09 g, 4.9 mmol) in 20 mL anhydrous dichloromethane was added triethylamine (1.70 mL, 2.5 equiv) and DMAP (0.61 g, 5.0 mmol), followed by di-*tert* butyl dicarbonate (2.15 g, 9.8 mmol) in small portions. After 4 days, the mixture was concentrated to dryness and purified by chromatography (ISCO, 40 g column, heptane/EA gradient) to afford 430 mg (27%) of **5a** and 690 mg (44%) of **6a**, along with some mixed fractions. Both compounds were recrystallized from heptane. Compound **5a**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.27 (d, 2H, *J* = 8.6 Hz), 7.13 (d, 2H, *J* = 8.2 Hz), 4.62 (br s, 1H), 3.37 (dd, 1H, *J* = 5.5, 9.2 Hz), 2.93 (dd, 1H, *J* = 1.5, 0.8 Hz), 2.37 (ddd, 1H, *J* = 2.3, 9.2, 11.5 Hz), 2.02–1.93 (m, 2H), 1.73 (ddd, 1H, *J* = 1.4, 1.4, 10.3 Hz), 1.52 (s, 9H). Compound **6a**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.30 (d, 2H, *J* = 8.4 Hz), 7.18 (d, 2H, *J* = 8.4 Hz), 4.46 (br s, 1H), 3.37–3.30 (m, 1H), 2.96–2.92 (m, 1H), 2.29–2.09 (m, 2H), 1.88 (d, 1H, *J* = 10.3 Hz), 1.65 (d, 1H, *J* = 10.5 Hz), 1.54 (s, 9H).

In conclusion, we have demonstrated a facile hydroarylation reaction of **1** with aryl iodides. Several reaction parameters were investigated resulting in conditions that allow for a slight regiochemical bias in the arylated products. The reaction is scalable, and only limited by the availability of the aryl iodide substrates. Future work, describing the ability to convert these lactams into a range of stereochemically defined amines, will be reported in due course.

### Acknowledgments

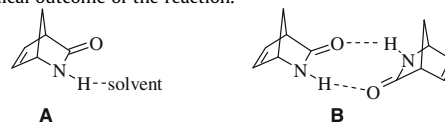
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8. Regiochemical assignments are in accord with those reported in Ref. 5.
9. Solvent effects on the regiochemistry of Pd-catalyzed hydroarylation of propiolamides have been observed, see: Hay, L. A.; Koenig, T. M.; Ginah, F. O.; Copp, J. D.; Mitchell, D. J. *Org. Chem.* **1998**, *63*, 5050.
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11. A tentative explanation for the solvent and concentration effects based on entries 2 and 7 can be offered at this time. However, additional experiments exploring a range of concentrations and aryl iodide substrates would be required for a more definitive explanation. Novak et al. have concluded from a combination of photoelectron spectroscopy and ab initio calculations that suggest that the olefin moiety in **1** is polarized solely by inductive effects exerted by the amide moiety.<sup>16</sup> Additionally, the partial charge distribution of **1** was generated with the B3LYP functional and 6-31G\*\* basis set using Jaguar (version 7.5, Schrödinger, LLC, New York, NY, 2008). Since the partial charges are dictated by the orbital electronegativity of the atoms, these values can be used as a guide that points toward the most electrophilic carbon.<sup>17</sup> In this case, the partial charge at C-6 (−0.25) was more negative than partial charge at C-5 (−0.15). Therefore, one would expect a higher degree of reactivity at the more

electrophilic carbon (C-5). The ability of the amide group to polarize the olefin would be expected to be influenced by the solvent and concentration. In polar solvents, the solvated monomeric amide **A** would be expected to be the predominant species. Similarly, at higher concentrations of **1** in non-polar solvents a hydrogen-bonded dimer **B** would be expected to predominate. At high dilution, the naked monomeric amide would be expected to predominate.<sup>18</sup> The amide would then be expected to exert its maximum effect on polarization of the olefin, leading to a greater influence on the regiochemical outcome of the reaction.



- The effect of remote substituents on the regioselectivity of the reductive arylation has been noted previously.<sup>18,3a</sup>
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  14. For related olefin substrates, we have noted that the reaction time can be shortened by microwave irradiation but yields were low due to competing Pd-catalyzed reduction of the aryl bromide with triethylammonium formate (C. Neagu, unpublished results).
  15. The hydroarylation reaction has been scaled using >30 g of 2-azabicyclo[2.2.1]hept-5-en-3-one to provide products with the equivalent yield and regioisomeric ratio.
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