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RHODIUM-CATALYZED ARYLATION OF 2-AZABICYCLO[2.2.1]HEPT-5-EN-3-ONE WITH ARYLBORONIC ACIDS UNDER MICROWAVE IRRADIATION

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Abstract – Rhodium-catalyzed arylation of 2-azabicyclo[2.2.1]hept-5-en-3-one was successfully performed by applying microwave irradiation.

Since the isolation of epibatidine possessing potential affinity to nicotinic acetylcholine (nACh) receptor,[1] the biological and pharmacological evaluation of this important class of compound, consisting of an aryl-azabicyclo[2.2.1]heptane system as a structural motif, has attracted much attention, and a large number of preeminent methods have been developed for the preparation of vast range of the derivatives.[2]

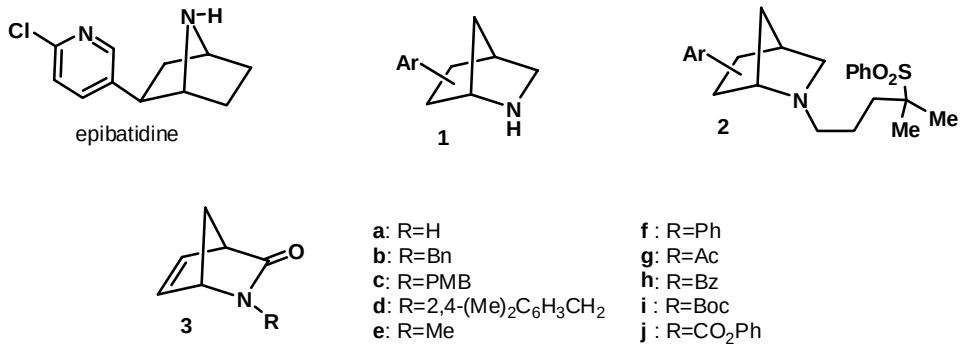
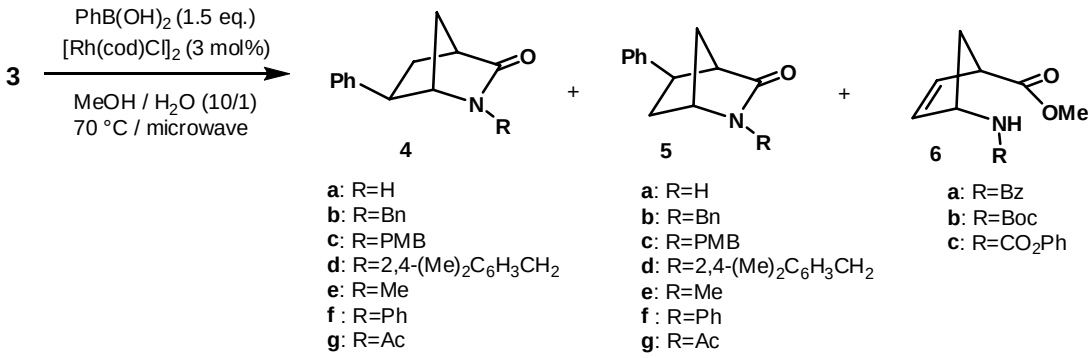


Figure 1. Azabicyclo[2.2.1]heptanes

Of various synthetic routes to aryl-2-azabicyclo[2.2.1]heptanes such as **1** (nACh receptor ligand)[3] and **2** (serotonin (5-HT7) receptor ligand),[4] one straightforward procedure involves the reductive Heck arylation of 2-azabicyclo[2.2.1]hept-5-ene with aryl halides. In connection with our recent interest in the chemical diversity of 2-azabicyclo[2.2.1]hept-5-en-3-one (**3**) associated with the strained bicyclic ring system

incorporating an amide group and a double bond,[5] the metal-catalyzed arylation of **3** was envisioned from a structural perspective to allow a rather practical and divergent approach to obtaining a variety of aryl-2-azabicyclo[2.2.1]heptanes. However, our initial attempt at performing the reductive Heck reaction of **3b** with iodobenzene proved to be unsuccessful and gave no arylation products due, in part, to the inherent poor reactivity of the double bond of **3b**.[6] Although considerable efforts have been recently made to develop an efficient catalytic system for the addition of organometallic reagents to alkenes,[7] catalytic arylation of the double bond of **3** has not been yet known. Prompted by this, we have focused our attention on the development of a catalytic procedure for the introduction of an aryl group at the double bond of **3**, and herein, we report the successful rhodium-catalyzed arylation of **3** with arylboronic acids through the application of dielectric heating (microwave irradiation).



Scheme 1

Initially, **3b** having *N*-benzyl group was subjected to the reaction with phenylboronic acid (1.5 equiv.) in the presence of $[Rh(COD)Cl]_2$ (3 mol%) and KOH (1 equiv.) in $MeOH/H_2O$ (in a volume ratio of 10/1) at 70 °C. However, this resulted in the formation of complex mixtures. In our previous report,[8] it was demonstrated that copper-catalyzed *N*-arylation of **3a** with arylboronic acids could be successfully promoted by taking advantage of microwave irradiation, so inquiries were made into whether the rhodium-catalyzed arylation of **3b** could be remedied by using this protocol. Then, irradiation of a mixture of **3b**, phenylboronic acid, KOH and a catalytic amount of $[Rh(COD)Cl]_2$ in $MeOH/H_2O$ was carried out in a microwave reactor at 70 °C, and the reaction readily proceeded within 0.5 h to produce **4b** and **5b** (in ratio of **4b**/**5b**=60/40) in 72% yield (Scheme 1). Table 1 shows the results from the arylation reaction of **3** having various *N*-substituents with phenylboronic acid, with the yields of **4** and **5** varying according to *N*-substituent. The most efficient conversion was realized with **3a**, and the reaction was complete within 0.5 h, producing **4a**[9] in preference to **5a** in 80% combined yield.[10] In contrast, only the ring-opening products **6a-c** were isolated from the reaction of **3h-j** having *N*-acyl groups through the

solvolysis of the amide group, except for the reaction of **3g** having an *N*-acetyl group, which provided **4g** and **5g** in low yield.

Table 1. Microwave-promoted reaction of **3** with phenylboronic acid in the presence of $[Rh(cod)Cl]_2$

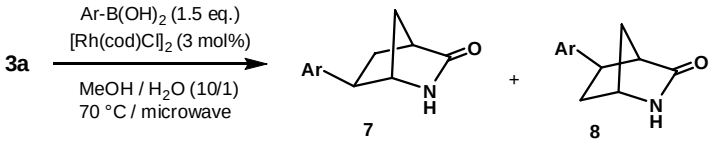
Entry	**3**	Time (h)	Yield (%)[a]
1	**3a**	0.5	80 (**4a**/**5a** = 75/25)[b]
2	**3b**	0.5	72 (**4b**/**5b** = 60/40)[b]
3	**3c**	0.5	40 (**4c**/**5c** = 80/20)[b]
4	**3d**	0.5	29 (**4d**/**5d** = 80/20)[b]
5	**3e**	0.5	71 (**4e**/**5e** = 60/40)[b]
6	**3f**	1	29 (**4f** /**5f** = 70/30)[b]
7	**3g**	0.5	28 (**4g**/**5g** = 30/70)[b]
8	**3h**	3	32 (**6a**)
9	**3i**	0.5	79 (**6b**)
10	**3j**	2	47 (**6c**)

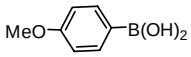
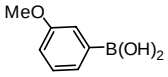
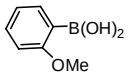
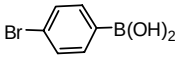
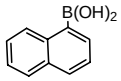
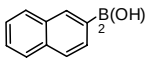
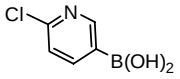
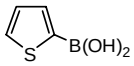
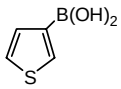
[a] Combined isolated yields based on **3**. [b] Ratio of **7**/**8** determined by 500 MHz ^{1}H-NMR analysis.

Next, **3a** was similarly exposed to the reaction with various arylboronic acids (1.5 equiv.) in the presence of $[Rh(cod)Cl]_2$ (3 mol%) in MeOH/H_2O (10/1) at 70 °C employing microwave irradiation, to yield **7a-f** and **8a-f** in 53 to 84% yields with the predominant formation of **7** over **8** (Table 2, Entries 1-6). Thus, the same conditions were applied to the reaction with heteroaryl boronic acids. The reaction of **3a** with 3-pyridylboronic acid failed and complex mixtures resulted. Otherwise, the same treatment of (6-chloro-3-pyridyl)boronic acid allowed the isolation of **7g** and **8g** in a combined yield of 65%, and the ratio reserved in favor of **7g**. When 2- and 3-thienylboronic acids were subjected to the reaction, the formation of **7h** and **7i** predominated over **8h** and **8i**, respectively (Table 2, Entries 8-9). The reaction mechanism for the present arylation reaction of **3** with arylboronic acids is explicable with reference to a common mechanism.[11] Although the interpretation for the preference of **4** and **7** over **5** and **8**, respectively, is not clear at the present, the intervention of a transannular nitrogen participation might be worthy of further investigation.[12]

In this paper, we have demonstrated the successful use of the microwave irradiation for the rhodium-catalyzed arylation reaction of **3** with arylboronic acids. Further studies, including an investigation of the mechanistic aspects and synthetic applicability of the reaction, are in progress.

Table 2. Microwave-promoted reaction of **3a** with arylboronic acids in the presence of $[Rh(cod)Cl]_2$



Entry	Ar-B(OH)$_2$	Time (h)	Yield (%)[a]
1		1.5	84 (**7a**/**8a** = 80/20)[b]
2		1.5	84 (**7b**/**8b** = 74/26)[b]
3		2.5	70 (**7c**/**8c** = 77/23)[b]
4		2	65 (**7d**/**8d** = 65/35)[b]
5		3	48 (**7e**/**8e** = 74/26)[b]
6		2	53 (**7f** /**8f** = 85/15)[b]
7		6	65 (**7g**/**8g** = 75/25)[b]
8		6	41 (**7h**/**8h** = 98/2)[b]
9		6	52 (**7i** /**8i** = 98/2)[b]

[a] Combined isolated yields based on **3**. [b] Ratio of **7**/**8** determined by 500 MHz ^{1}H-NMR analysis.

ACKNOWLEDGEMENTS

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9. The structure of **4a** was confirmed by X-ray crystal structure. Crystallographic data (excluding structure factors) for **4a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 687581. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.UK).
10. **Typical procedure: the reaction of 3a with phenyl boronic acid.** To a solution of **3a** (0.4 mmol), phenylboronic acid (0.6 mmol) and $[Rh(cod)Cl]_2$ (0.012 mmol) in MeOH/H_2O (v/v = 10/1, 2 mL) was added pulverized KOH (0.4 mmol). The yellow reaction mixture was stirred for 5 min at rt, and then irradiated in microwave reactor for 0.5 h at 70 °C. After cooling, the reaction mixture was diluted with EtOAc, washed with 10% NaOH and brine, and the organic layer was dried over $MgSO_4$. The solvent was removed and the residue was purified by silica gel column chromatography (hexane:EtOAc = 3:1) to provide **4a** and **5a**.

    (*rel*)-(1*S*,4*S*,6*R*)-6-Phenyl-2-azabicyclo[2.2.1]heptan-3-one (4a): Mp 86-87 °C. IR ($CHCl_3$): 3432,

3196, 1690 cm^{-1}. ^{1}H-NMR (500 MHz, ppm, $CDCl_3$) δ: 7.33 (t, 2H, *J* = 7.4 Hz), 7.21-7.24 (m, 3H), 6.18 (br s, 1H), 3.90 (s, 1H), 3.26 (dd, 1H, *J* = 5.7, 7.9 Hz), 2.83 (d, 1H, *J* = 2.9 Hz), 2.16 (ddd, 1H, *J* = 2.1, 9.3, 13.0 Hz), 2.08 (dt, 1H, *J* = 4.5, 13.2 Hz), 1.95 (dt, 1H, *J* = 1.7, 10.3 Hz), 1.78 (dd, 1H, *J* = 1.8, 9.7 Hz). ^{13}C-NMR (126 MHz, ppm, $CDCl_3$) δ: 181.4, 142.1, 128.7, 127.3, 126.6, 60.6, 48.7, 45.0, 38.5, 30.9. HR-EI-MS *m/z*: Calcd for $C_{12}H_{13}NO$ (M^+): 187.0997. Found: 187.0982.

(*rel*)-(1*R*,4*R*,5*R*)-5-Phenyl-2-azabicyclo[2.2.1]heptan-3-one (5a): IR ($CHCl_3$): 3436, 3204, 1682 cm^{-1}. ^{1}H-NMR (500 MHz, ppm, $CDCl_3$) δ: 7.32 (t, 2H, *J* = 8.1 Hz), 7.24-7.25 (m, 2H), 7.22 (m, 1H), 5.61 (br s, 1H), 4.02 (s 1H), 3.33 (dd, 1H, *J* = 5.2, 8.6 Hz), 2.88 (s, 1H), 2.25 (ddd, 1H, *J* = 2.2, 9.0, 12.5 Hz), 2.05 (ddd, 1H, *J* = 2.3, 4.5, 12.4 Hz), 1.99 (d, 1H, *J* = 11.5 Hz), 1.82 (dd, 1H, *J* = 1.2, 10.3 Hz). ^{13}C-NMR (126 MHz, ppm, $CDCl_3$) δ: 180.95, 142.82, 128.74, 127.24, 126.60, 55.85, 51.28, 41.51, 38.89, 38.72. HR-EI-MS *m/z*: Calcd for $C_{12}H_{13}NO$ (M^+): 187.0997. Found: 187.1013.

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