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

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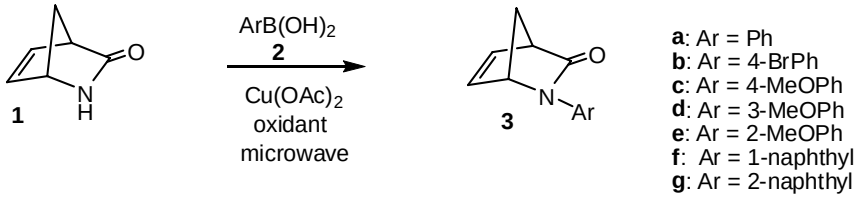
Abstract – Copper-catalyzed *N*-arylation reaction of 2-azabicyclo[2.2.1]hept-5-en-3-one (ABH) with arylboronic acids was successively performed in the presence of KOH and trimethylamine-*N*-oxide under microwave irradiation.

Because of its diverse chemical lability attributable to the bicyclo[2.2.1]heptene ring system involving the amide group,[1] we have envisioned that 2-azabicyclo[2.2.1]hept-5-en-3-one (ABH) (**1**) would have wide-spread utility in the design of synthetic process for natural isolates and medicinal agents.[2] One of the most conspicuous chemical features of **1** consists in the transannular participation between the nitrogen and the double bond system.[3] During our studies, we have disclosed that the nature of the *N*-substituent of **1** was extremely important to improve the regioselectivity in the ruthenium-catalyzed ring-opening cross-metathesis reaction with allyltrimethylsilane[4] or the rhodium-catalyzed coupling reaction with arylboronic acids.[5] To gain further insight into this participation, we next set about to investigate the effect of the *N*-aryl group on transannular participation in **1**, and thus, a short and reliable preparation of *N*-aryl ABH (**3**) became the first subject of our study.

Although a wealth of procedures for the metal-catalyzed *N*-arylation of the amide groups have already appeared,[6] there has been only two reports, to our knowledge, on the direct *N*-arylation of **1**, that is, the copper-mediated reaction with phenylboronic acid or triphenylbismuth, in which $Cu(OAc)_2$ in amounts equimolar with **1** is required and the reaction is restricted to the use of phenylboronic and (4-methylphenyl)boronic acids.[7]



Scheme 1

After several attempts to obtain **3**, we eventually developed an efficient protocol for the direct introduction of aryl groups to the nitrogen of **1** based on the microwave-assisted reaction with arylboronic acids (**2**) in the presence of $Cu(OAc)_2$ (0.1 equiv.), as described in Scheme 1.

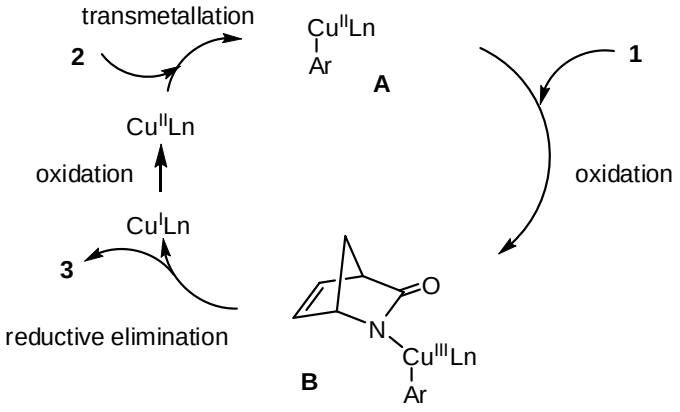
The copper-mediated reaction of **1** with phenylboronic acid (**2a**) has become of our primary interest, and let us to reinvestigate the precedent for the production of **3a**,[7] which indicated the reproducibility of the low yield (Table 1, Run 1). During these studies, we somewhat surprisingly found a pronounced acceleration in the reaction when CH_2Cl_2 was simply replaced by MeCN (Table 1, Run 2).

Table 1 *N*-Phenylation of **1** with phenylboronic acid (**3a**)[a]

Run	$Cu(OAc)_2$	Base	Oxidant	Solvent	Conditions	**3a** (%)[h]
1	1 equiv.	Et_3N[b]	none[d]	CH_2Cl_2	rt, 60 h	19[7]
2	1 equiv.	Et_3N[b]	none[d]	MeCN	rt, 60 h	70
3	1 equiv.	Et_3N[b]	none[d]	MeCN	80 °C, 60 h	92
4	1 equiv.	Et_3N[b]	pyridine-N(O)[e]	MeCN	rt, 48 h	44
5	1 equiv.	Et_3N[b]	$Me_3N(O)$[f]	MeCN	rt, 20 h	90
6	0.1 equiv.	Et_3N[b]	$Me_3N(O)$[f]	MeCN	rt, 48 h	9
7	0.1 equiv.	Et_3N[b]	$Me_3N(O)$[f]	MeCN	80 °C, 0.5 h, MW[g]	38
8	0.1 equiv.	KOH[c]	$Me_3N(O)$[f]	MeCN	80 °C, 0.5 h, MW[g]	85

[a] 2 equiv. [b] 2 equiv. [c] pulverized KOH (5 equiv.) [d] Under air [e] Pyridine-*N*-oxide (1.1 equiv.) [f] Trimethylamine-*N*-oxide (1.1 equiv.) [g] Microwave irradiation [h] Isolated yields of **3a**

The present copper-mediated *N*-arylation process could be rationalized in terms of a common path in Scheme 2,[8] where the reaction process is evidently dependent on the availability of Cu(III) species (**B**) *in situ* through the oxidation of Cu(II) species (**A**). Therefore, treatment of **1** with **2a** in the presence of $Cu(OAc)_2$ (1 equiv.) and Et_3N (2 equiv.) at room temperature became apparent to entail the formation of **3a** in fairly high yield with the aid of trimethylamine-*N*-oxide (1.1 equiv.) (Table 1, Run 5).



Scheme 2

Having succeeded in generation of **3a** by the use of $Cu(OAc)_2$ (1 equiv.), our interest was then denoted to see if these results were adequate for the copper-catalyzed *N*-arylation process. As seen in Table 1 (Run 6), a simple reduction in the amount of $Cu(OAc)_2$ did not affect the catalytic reaction, resulting in the formation of a small amount of **3a** and the recovery of substantial amounts of **1**. Eventually, adaptation of microwave conditions for the development of the catalytic reaction was found to be valid.[9] On performing the reaction of **1** and **2a** under microwave irradiation in the presence of catalytic amounts of $Cu(OAc)_2$ (0.1 equiv.), pulverized KOH (5 equiv.) and $Me_3N(O)$ (1.1 equiv.) in MeCN, the reaction time could be dramatically reduced to 30 min with a significant increase in the yield of **3a** (Table 1, Run 8).[10]
Furthermore, **1** was subjected to the reaction with a variety of arylboronic acids **2** under the optimized conditions, providing **3** in moderate to good yields, and these results are summarized in Table 2.

Table 2 Microwave-assisted *N*-arylation of **1**[a]

Run	**2**	Time (h)	**3** (%)[b]
1	**2b** (Ar = 4-BrPh)	1.5	69 (**3b**)
2	**2c** (Ar = 4-MeOPh)	0.5	72 (**3c**)
3	**2d** (Ar = 3-MeOPh)	0.5	83 (**3d**)
4	**2e** (Ar = 2-MeOPh)	1.0	58 (**3e**)
5	**2f** (Ar = 1-naphthyl)	1.0	70 (**3f**)
6	**2g** (Ar = 2-naphthyl)	0.5	54 (**3g**)

[a] A mixture of **1**, **2** (2 equiv.), pulverized KOH (5 equiv.), $Cu(OAc)_2$ (0.1 equiv.) and $Me_3N(O)$ (1.1 equiv.) in MeCN was heated at 80 °C under microwave irradiation [b] Isolated yields of **3**

In summary, we have demonstrated herein a concise and reliable procedure for the formation of **3** by way of the microwave-assisted *N*-arylation of **1** with **2** using a catalytic amount of $Cu(OAc)_2$.

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9. Microwave (MW) irradiation (300 W) was carried out in a glass tube using a Green-Motif I (IMCR-25003) monomode microwave reactor (IDX Corporation).
10. **Typical Procedure:** To a solution of **1** (0.4 mmol), phenylboronic acid (0.8 mmol) and $Cu(OAc)_2$ (0.04 mmol) in MeCN (2 mL), trimethylamine-*N*-oxide (0.44 mmol) and pulverized KOH (2.0 mmol) were added. After stirring for 5 min at rt, the mixture was heated at 80 °C for 0.5 h under microwave irradiation. After insoluble materials were removed by filtration, the filtrate was concentrated *in vacuo*, and the residue was extracted with AcOEt. The extract was washed with 10% NaOH, water and brine, and dried over $MgSO_4$. The solvent was removed, and the residue was separated by silica gel column chromatography (hexane:AcOEt=10:1) to give **3a** in 85% yield.
(*rel*)-(1*S*,4*R*)-2-Phenyl-2-azabicyclo[2.2.1]hept-5-en-3-one (3a): IR (neat): 1698 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.27 (dd, 1H, *J* = 2.3, 8.0 Hz), 2.48 (dd, 1H, *J* = 3.4, 8.0 Hz), 3.50 (s, 1H), 4.77 (s, 1H), 6.72 (m, 1H), 7.02 (m, 1H), 7.09 (m, 1H), 7.32-7.35 (m, 2H), 7.37-7.39 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: 54.8, 57.3, 64.7, 118.7, 124.0, 129.0, 138.5, 139.1, 157.3, 177.4. HR-MS *m/z*: Calcd for $C_{12}H_{11}NO$: 185.0841. Found: 185.0845.