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KO^{t}Bu Mediated Synthesis of Phenanthridinones and Dibenzoazepinones

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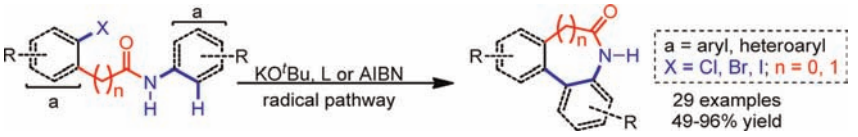
ABSTRACT



Synthesis of substituted phenanthridinones and dibenzoazepinones has been realized from 2-halo-benzamides in the presence of potassium *tert*-butoxide and a catalytic amount of 1,10-phenanthroline or AIBN. This new carbon−carbon bond forming reaction gives direct access to various biaryl lactams containing six- and seven-membered rings chemoselectively. Carbon−carbon coupling seems to proceed by the generation of a radical in the amide ring which leads to C−H arylation of aniline.

The search for a novel method to construct biaryls is a topic of current interest in academia. Although the Pd-catalyzed carbon−carbon coupling reaction is one of the most reliable methods for synthesizing biaryls, considerable effort is being made to develop palladium-free approaches for the synthesis of biaryls due to a substantial increase in the price of palladium over the past five years. Among these palladium-free approaches, the catalytic system using less expensive metals like Cu, Fe, Co, and Ni or bases such as MO*t*Bu (M = Na, K)/ligand mediated C−C coupling via C−H arylation of arenes, has attracted considerable interest for the construction of biaryls. Recently potassium *tert*-butoxide mediated inter- and intramolecular arylation of various substituted arenes has been reported.[1,2] For the first time, here we report a potassium *tert*-butoxide mediated intramolecular carbon−carbon coupling reaction through C−H arylation of an aniline ring for the synthesis of biologically active phenanthridinones and related lactams. By using this alternative chemical reaction, six-membered phenanthridinone and seven-membered dibenzoazepinone biaryl lactams can be generated under mild reaction conditions from 2-halo-benzamide substrates using potassium *tert*-butoxide and a catalytic amount of 1,10-phenanthroline or azoisobutylonitrile (AIBN) eq 1.

Biaryl lactams are privileged cores present in many alkaloids and pharmaceutically relevant organic molecules.[3,4] Earlier reported synthetic protocols involve a multistep strategy for the construction of phenathridinones and related lactams. Palladium-catalyzed biaryl coupling is one of the key steps in the construction of phenanthridinones.[5−8] Recently a palladium-catalyzed

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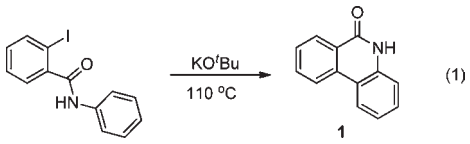
one pot synthetic strategy was realized from *N*-methoxybenzamides and aryl iodide/arene coupling partners.[7c,d] Charette et al. have reported an example of *N*-benzyl phenanthridinone from a *N*-methyl-*N*-(2-iodophenyl)-benzamide substrate.[2c] Nonetheless, these one pot protocols have been reported only for the synthesis of six-membered biaryl lactams.[5−7] Moreover, deprotection of N−R (R = benzyl, methoxy) to N−H is required after biaryl coupling in most of these methodologies.[3b,5a,5b,8c,8d]

Recently, we have developed a copper catalyzed Se/S−N bond forming reaction from 2-halo-benzamides and selenium/sulfur powder.[9] Serendipitously, formation of phenanthridinone **1** is observed while attempting the isolation of a copper−amide complex. It is worth noting that the formation of **1** occurred even without the addition of copper. In continuation of our work on coupling reactions using 2-halo-arylamide substrates, here, we disclose a new KO^{t}Bu mediated C−C coupling reaction in 2-halo-benzamides.

Optimization of reaction conditions is briefly summarized in Table 1. The yield of coupled product **1** was very low when the reaction was carried out in DMSO and DMF despite the complete conversion of the substrate. The reaction gave better a yield of phenanthridinone **1** from 2-iodo-*N*-phenylbenzamide in solvents such as benzene, xylene, and mesitylene (Table 1, entriy 2). Various bases such as K_2CO_3, KOH, NaOH, and ^{n}BuLi were also screened for the optimization of reaction conditions, but KO^{t}Bu was found to be a better base for the promotion of coupling reactions. Next, ligands such as TMEDA, DMEDA, ethylenediamine (ene), and 1,10-phenanthroline were screened in the reaction (entries 6−8, Table 1). In the presence of TMEDA, DMEDA, pyridine, and ene, the reaction was sluggish and a poor yield of the coupled product was obtained. 1,10-Phenanthroline provides a 90% yield of coupled product. KO^{t}Bu alone is not effective for the C−C coupling, as only 35% of product was formed in 24 h and 60% of the unreacted substrate was recovered from the reaction. When 0.2 equiv of a radical initiator, AIBN, was employed, the coupled product was obtained in excellent yield (Table 1, entry 5).

Table 1. Optimization of Reaction Conditions[a]



(1)

1

entry	M/ligand	solvent	t (h)	subs. conv. (%)	**1** (%)
1	CuI/L[b]	DMF	24	100	20
2	CuI/L	benzene	14	100	45
3	**–/L**	**benzene**	**14**	**97**	**90**[c]
4	**–/L/AIBN**[d]	**benzene**	**7**	**100**	**96**
5	–/AIBN[d]	benzene	6	100	96
6	–/TMEDA	benzene	24	40	20
7	–/pyridine	benzene	24	10	<10
8	–/ene	benzene	24	<5	trace

[a] Reaction was carried out at a 1 mmol scale using 5 equiv of KO^{t}Bu. L = 1,10-phenanthroline. [b] 20 mol % of CuI/L was used. [c] Trace of decoupled product was observed. [d] 0.2 equiv of AIBN was used.

After extensive screening, we chose KO^{t}Bu (5−7 equiv) and 1,10-phenathroline (20 mol %) or AIBN (0.2 eqiv) and benzene/mesitylene as a solvent to study the substrate scope and limitation of the reaction. Synthesized phenanthridinones and related lactams are presented in Table 2. Phenanthridinone **1** was obtained in 96%, 70%, and 49% yield from 2-iodo-, 2-bromo-, and 2-chloro-benzamides, respectively. Substrates with an electron-withdrawing fluoride, difluoride, chloride, bromide or the donating group methyl, methoxy, and dimethoxy on either aryl ring were tolerated under our reaction conditions (entries 2−8, Table 2). Further, the scope of the reaction extended to different aryl substrates. Naphthalene and thiophene based 2-halo-arylamide substrates were successfully utilized to form coupled products **9**−**10** and **28** under optimized reaction conditions. Pyridine as an amidic ring failed to undergo a C−C coupling reaction. Instead, hydroxylation of 2-bromo-*N*-phenyl-nicotinamide was observed (see Supporting Information, pp S31−32). However, pyridine as an amine ring coupled to form desired product **29** in good yield (Table 3 entry 13). After studying the synthesis of six-membered phenanthridinones **1**−**10** and **18**−**29** (*vide infra*), we turned our attention to seven-membered dibenzoazepinones. Worthy of note, 2-(2-iodophenyl)-*N*-phenylacetamide substrates underwent a C−C coupling

(5) For Pd-catalyzed construction of phenanthridinone skeletons, see: (a) Ferraccioli, R.; Carenzi, D.; Rombola, O.; Catellani, M. *Org. Lett*. **2004**, *6*, 4759. (b) Furuta, T.; Kitamura, Y.; Hashimoto, A.; Fujii, S.; Tanaka, K.; Kan, T. *Org. Lett*. **2007**, *9*, 183. (c) Bernini, R.; Cacchi, S.; Fabrizi, G.; Sferrazza, A. *Synthesis* **2008**, 729. (d) Maestri, G.; Larraufie, M.-H.; Derat, E.; Ollivier, C.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Org. Lett*. **2010**, *12*, 5692. (e) Zhang, L.; Ang, G. Y.; Chiba, S. *Org. Lett*. **2010**, *12*, 3682. (f) Budén, M. E.; Dorn, V. B.; Gamba, M.; Pierini, A. B.; Rossi, R. A. *J. Org. Chem*. **2010**, *75*, 2206. (g) Korivi, R. P.; Cheng, C.-H. *Chem.—Eur. J*. **2010**, *16*, 282. (h) Abe, H.; Kobayashi, N.; Takeuchi, Y.; Harayama, T. *Heterocycles* **2010**, *80*, 873. (i) Donati, L.; Michel, S.; Tillequin, F.; Porée, F.-H. *Org. Lett*. **2010**, *12*, 156. (j) Dubost, E.; Magnelli, R.; Cailly, T.; Legay, R.; Fabis, F.; Rault, S. *Tetrahedron* **2010**, *66*, 5008. (k) Donati, L.; Leproux, P.; Prost, E.; Michel, S.; Tillequin, F.; Gandon, V.; Porée, F.-H. *Chem.—Eur. J*. **2011**, *17*, 12809. (l) Blanchot, M.; Candito, D. A.; Larnaud, F.; Lautens, M. *Org. Lett*. **2011**, *13*, 1486.

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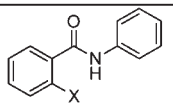
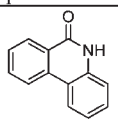
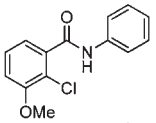
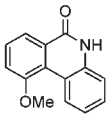
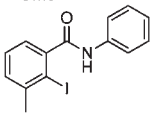
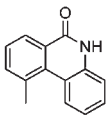
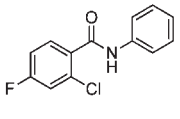
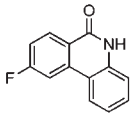
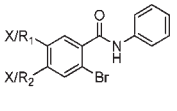
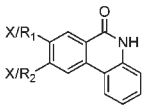
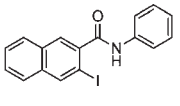
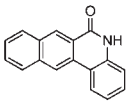
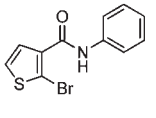
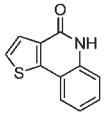
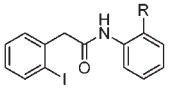
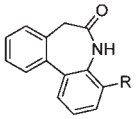
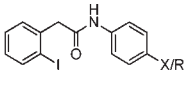
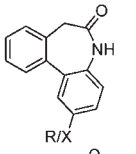
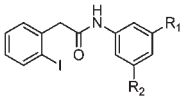
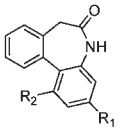
(7) (a) Lv, P.; Huang, K.; Xie, L.; Xu, X. *Org. Biomol. Chem*. **2011**, *9*, 3133. (b) Lee, S.; Hwang, S.; Yu, S.; Jang, W.; Lee, Y. M.; Kim, S. *Arch. Pharm. Res*. **2011**, *34*, 1065–1070. (c) Wang, G.-W.; Yuan, T.-T.; Li, D.-D. *Angew. Chem., Int. Ed*. **2011**, *50*, 1380. (d) Karthikeyan, J.; Cheng, C.-H. *Angew. Chem., Int. Ed*. **2011**, *50*, 9880.

(8) Seven-membered biaryl lactams: (a) Baudoin, O.; Cesario, M.; Guénard, D.; Guéritte, F. *J. Org. Chem*. **2002**, *67*, 1199. (b) Fauq, A. H.; Simpson, K.; Maharvi, G. M.; Golde, T.; Das, P. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 6392. (c) Tabata, H.; Akiba, K.; Lee, S.; Takahashi, H.; Natsugari, H. *Org. Lett*. **2008**, *8*, 4871. (d) Tabata, H.; Suzuki, H.; Akiba, K.; Takahashi, H.; Natsugari, H. *J. Org. Chem*. **2010**, *75*, 5984. (e) Pan, X.; Wilcox, C. S. *J. Org. Chem*. **2010**, *75*, 6445.

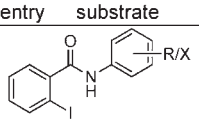
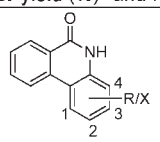
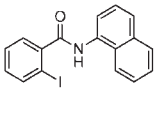
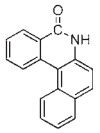
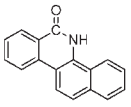
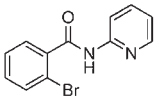
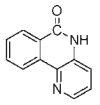
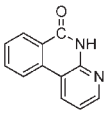
(9) (a) Balkrishna, S. J; Bhakuni, B. S.; Chopra, D.; Kumar, S. *Org. Lett*. **2010**, *12*, 5394. (b) Balkrishna, S. J.; Bhakuni, B. S.; Kumar, S. *Tetrahedron* **2011**, *67*, 9565. (c) Bhakuni, B. S.; Balkrishna, S. J.; Kumar, A.; Kumar, S. *Tetrahedron Lett*. **2012**, *53*, 1354. (d) For C−O Coupling, see: Balkrishna, S. J.; Kumar, S. *Synthesis* **2012**, *44*, 1417.

Table 2. KO^{t}Bu-Mediated Synthesis of Biaryl Lactams

entry	substrate	product	yield (%)[a]
1a			**1** (96) X, I
1b			**1** (70) X, Br
1c			**1** (49) X, Cl
2			**2** (49)
3			**3** (70)
4			**4** (66)
5			**5** R_1, OMe, R_2, H(82)
6			**6** X, F, R_2, H (62)
7			**7** X, F (86)
8			8 R, OMe (84)
9			**9** (90)
10			**10** (75)
11			**11** R, H (84)
12			**12** R, OMe (72)
13			**13** X, F (76))
14			**14** X, Br (60)
15			**15** R, OMe (82)
16			**16** R_1, OMe, R_2,H (83)
17			**17** R_1, R_2, OMe (87)

[a] Yield obtained using 1 mmol of substrate, 0.2 equiv of AIBN or 1,10-phenanthroline, and 5−7 equiv of KO^{t}Bu. AIBN and 1,10-phenanthroline were used for compounds **1**−**10** and **11**−**18**, respectively. Structures of **12**−**17** were predicted based on a crystal structure study.

Table 3. Regioselective Cyclization on Substituted Aniline

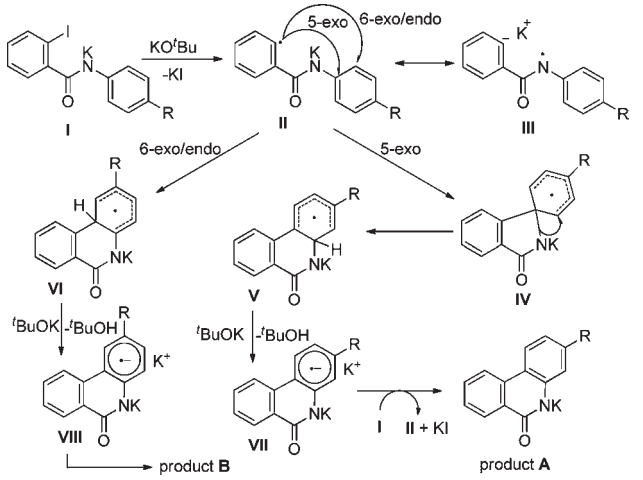
entry	substrate	product yield (%)[a] and ratio[b,c]
		
1	R, *ortho*-OMe	**18** R, 1-OMe (87)
2	X, *ortho*-F	**19a** X, 1-F and **19b** X, 3-F (84) (3.5:1)
3	X, *ortho*-Cl	**20a** X, 1-Cl and **20b** X, 3-Cl (81) (3.1:1)
4	X, meta-F	**21** X, 2-F and **19b** 3-F (70) (1:1)
5[d]	R, meta-OMe	**18** R, 1-OMe (38) and **22** 3-OMe (35) (1:1)
6	X, *para*-F	**21** X, 2-F (81)
7	X, *para*-Cl	**23** X, 2-Cl (83), (87)[e]
8	X, *para*-Br	**24** X, 2-Br (70)
9	R, *para*-OMe	**25** 2-OMe and **22** 3-OMe (90),(83)[e] (1:1)[a,e]
10	R, para-Me	**26a** 2-Me and **26b** 3-Me (95),(89)[d] (1:1)[a,e]
11	R, meta-diOMe	**27** R, 2,4-diOMe (88)
		 
12		**28a** and **28b** (74) (9.5:1)
		 
13		**29a** and **29b** (80) (5.1:1)

[a] Yield obtained using 1,10-phenanthroline (20 mol %) and KO^{t}Bu (5−7 equiv). [b] Ratio of isomers was determine by ^{1}H NMR. [c] Isomers were identified by comparison with reported data and 1D NOE experiments on **22**, **25**, **26a**, and **26b**. [d] Both isomers separated. [e] Ratio and yield were obtained by using AIBN and KO^{t}Bu.

reaction chemoselectively to form seven-membered dibenzoazepinones (**11**−**17**) under our reaction conditions, despite the possibility of a C−N coupling reaction. From our literature survey, it seems that synthesis of seven-membered dibenzoazepinones involved multisteps including Pd-catalyzed biaryl coupling as one of the key steps.[8] Moreover, present multistep methods have only been applied to the synthesis of dibenzoazepinones with unsubstituted aniline rings.[8a,c,e] Under our reaction conditions, several seven-membered dibenzoazepinones with a substituted aniline ring were obtained in one pot (entries 11−17, Table 2).

Variation of the substitution in the aniline ring is documented in Table 3 to study the regioselective outcome in the coupling reaction. Substrates with an ortho-substituted aniline ring gave a 5-*exo* regioisomer as the major product (entries 1−3, Table 3). Substrates with a meta-substituted aniline ring produced 5-*exo* and 6-*exo*/*endo* regioisomers in a 1:1 ratio. It seems that the selectivity is not influenced by the nature of the substituent at the meta position, as the ratio remains unchanged in the presence of an electron-withdrawing F and a donating methoxy substituent. Interestingly substrates with electron-withdrawing substituents in the aniline ring at the para position gave the 6-*exo*/*endo* product exclusively whereas substrates with electron-donating $-CH_3$ and $-OCH_3$ substituents gave both regioisomers (entries 6−10, Table 3). *N*-1-Naphthyl and *N*-2-pyridyl substrates gave 5-*exo* and 6-*exo*/*endo* regioisomers in 9.5:1 and 5.1:1 ratios, respectively. In the case of seven-membered analogues **11**−**17** only one regioisomer was observed regardless of the position and the nature of the substituent in the aniline ring (entries 12−17, Table 2). The regiochemistry of seven-membered dibenzoazepinone **12** was also established by

Scheme 1. Proposed Mechanism for C−H Arylation of Aniline



single crystal X-ray studies (see Figure S5 in the Supporting Information).

As the position of the substituent in the aniline ring remains unchanged in the substrates and seven-membered biaryl lactams (entries 12−17, Table 2), it seems that formation of a seven-membered ring occurred by 7-exo/*endo-trig* radical cyclization.

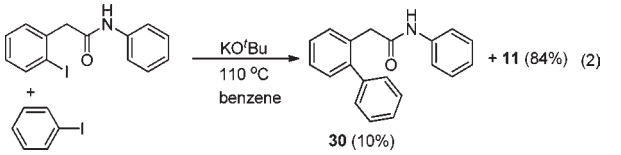
A possible reaction mechanism is depicted in Scheme 1 for the KO^{t}Bu-mediated C−C coupling reaction in 2-halobenzamides. Carbon−carbon coupling occurred smoothly in the presence of radical initiator AIBN, and the presence of radical was also confirmed by EPR spectroscopy in the reaction mixture (please see Supporting Information for EPR experiment). In conclusion, we believe that this is a radical pathway by which C−H arylation of the aniline ring occurrs.[1g,2c,10] The first step seems to be deprotonation of N−H by KO^{t}Bu leading to intermediate **I** as studied by ^{1}H NMR. The next step could be the generation of radical **II** by KO^{t}Bu to initiate the radical process.

To gain insight into the generation of the radical step, whether the radical is generated in the aniline or amide ring, a control experiment was carried out between 2-iodobenzamide and iodobenzene vs benzene (eq 2, Scheme 2). Only one cross-coupled product, **30**, was observed and arylation of the aniline ring was not detected, thereby suggesting the generation of the radical in the amide ring as presented in Scheme 2.

Generated carbon centered radical **II** in an amide ring seems to be stabilized by the −C(O)NH functionality leading to intermediate **III**. The 2-iodo-*N*-methyl-*N*-phenylbenzamide substrate lacking the N−H proton gave

(10) Rossi, R. A.; Pierini, A. B.; Peñéñory, A. B. *Chem. Rev.* **2003**, *103*, 71.

Scheme 2. Control Experiment on 2-Iodobenzamide



only 28% of the *N*-methyl analogue of **1** and the rest of the substrate converted into the decoupled product under optimized reaction conditions (please see Supporting Information for control experiment, p S34). Therefore it is reasonable to assume that the presence of N−H is crucial for the complete conversion of the substrate into the C−C coupled product. Radical **II** could attack on the aniline ring in an 6-*exo*/*endo-trig* or 5-*exo-trig* fashion leading to intermediates **IV** and **VI** respectively. Ring expansion in the intermediate **IV** would give the more stable hexadienyl radical **V**. Intermediates **V** and **VI** could be deprotonated in the presence of KO^{t}Bu leading to anion radicals **VII** and **VIII**, respectively.[10] In the last step, these radical anions would undergo electron transfer with intermediate **I** to give respective products, KI, and new radical **II**, thus continuing the radical chain with concomitant release of the product.

In summary, we have developed a simple palladium-free approach for the synthesis of phenanthridinone and related biaryl lactams from readily available 2-halo-benzamides. The use of KO^{t}Bu and a catalytic amount of 1,10-phenanthroline or AIBN is enough to obtain a high yield of the coupled product by the C−H arylation of the aniline ring. Most importantly, a one pot synthesis of seven-membered dibenzoazepinones from 2-halo-arylamides offers a unique process to traditional Pd-catalyzed reactions. Studies for a further understanding of this reaction and its application for the synthesis of other classes of organic molecules are underway in our laboratory.

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Supporting Information Available. Experimental details, characterization data for compounds, and CIF file for **12** (CCDC No. 870848). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.