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Practical Synthesis of Quinoxalinones via Palladium-Catalyzed Intramolecular N-Arylations

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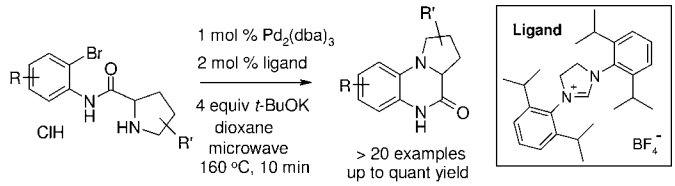
ABSTRACT



A practical and highly efficient route to the synthesis of pharmaceutically interesting quinoxalinone scaffolds is reported. The key step involves an intramolecular palladium-catalyzed N-arylation under microwave irradiation. The developed methodology tolerates a variety of bromoanilides to afford a diverse collection of bicyclic and polycyclic quinoxalinones in high yield.

Quinoxalinone core **1** (Figure 1) is commonly found in compounds displaying a variety of medicinal properties, such as antimicrobial, anticancer, anxiolytic, analgesic, antispastic, antiallergic, and antithrombotic activity.[1] Examples of quinoxalinones that have been in human clinical testing include the anxiolytic agent **2** (Panadiplon, $GABA_A$ partial agonist),[2] the neuroprotective agent **3** (YM872, AMPA antagonist),[3] and anti-HIV-1 reverse transcriptase inhibitors **4** (S-2720),[4] **5** (HBY-097),[5] and **6** (GW-420867X).[6]

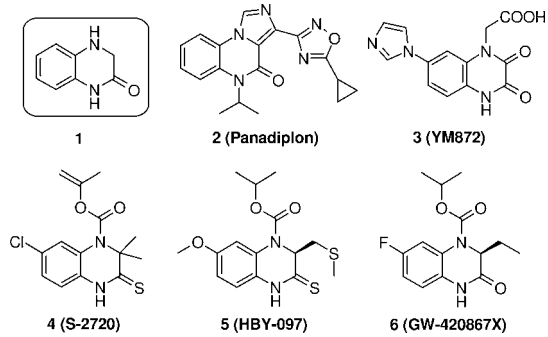


Figure 1. Biologically active compounds developed into clinical trials with quinoxalinone as a privileged structure.

Despite broad medicinal chemistry interest in this core, there are relatively few synthetic routes leading to quinoxalinones.[1] Taking the tricyclic quinoxalinone **7** as an example, one of the traditional synthetic approaches to this scaffold is based on the S_NAr reaction followed by reductive cyclization. This approach requires harsh conditions and

(1) For recent reviews of chemistry, biological properties, and SAR analysis of quinoxalinone scaffolds, see: (a) Li, X.; Yang, K.; Li, W.; Xu, W. *Drugs Future* **2006**, *31*, 979–989. (b) Carta, A.; Piras, S.; Loriga, G.; Paglietti, G. *Mini-Rev. Med. Chem.* **2006**, *6*, 1179–1200.

(2) Tang, A. H.; Franklin, S. R.; Hmes, C. S.; Ho, P. M. *J. Pharmacol. Exp. Ther.* **1991**, *259*, 248–254.

(3) (a) Takahashi, M.; Ni, J. W.; Kawasaki-Yatsugi, S.; Toya, T.; Yatsugi, S. I.; Shimizu-Sasamata, M.; Koshiya, K.; Shishikura, J. I.; Sakamoto, S.; Yamagouchi, T. *J. Pharmacol. Exp. Ther.* **1998**, *284*, 467–73. (b) Akins, P. T.; Atkinson, R. P. *Curr. Med. Res. Opin.* **2002**, *18*, 9–13.

(4) Balzarini, J.; Karlsson, A.; Meichsner, C.; Paessens, A.; Riess, G.; De Clercq, E.; Kleim, J. P. *J. Virol.* **1994**, *68*, 7986–7992.

(5) Balzarini, J.; Pelemans, H.; Riess, G.; Roesner, M.; Winkler, I.; De Clercq, E.; Kleim, J. P. *J. Infect Dis.* **1997**, *176*, 1392–1397.

(6) Balzarini, J.; De Clercq, E.; Carbonez, A.; Burt, V.; Kleim, J. P. *AIDS Res. Hum. Retroviruses* **2000**, *16*, 517–528.

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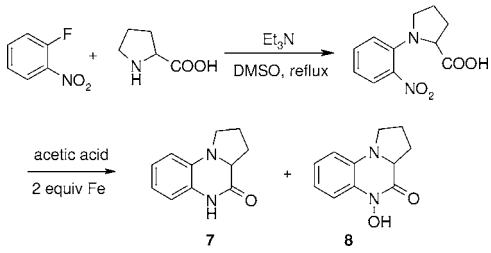
thereby precludes the use of many functionalities. Furthermore, this route often leads to the formation of undesired byproduct such as the *N*-hydroxide **8** (Scheme 1).[7] Hence,

Scheme 1. Conventional Synthetic Approach to Quinoxalinone **7**

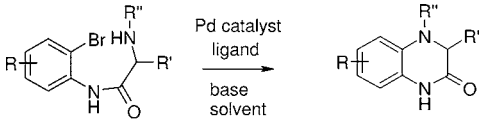


there is a need for new methodology that would allow access to a range of custom-designed quinoxalinones.

The transition-metal-catalyzed N-arylation reaction (Buchwald−Hartwig amination) has gained a lot of attention in recent years. The popularity of this approach may be attributed to mild conditions that are generally required to make *N*-aryl bonds, as well as compatibility to diverse functional groups.[8] Moreover, intramolecular N-arylation has been shown to be an attractive method to form polyheterocycles.[9]

Herein, we report a practical and highly efficient route to quinoxalinone scaffolds via palladium-catalyzed intramolecular N-arylation (Scheme 2).

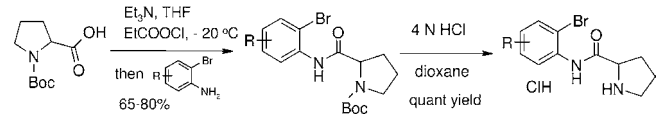
Scheme 2. Synthesis of Quinoxalinones via Palladium-Catalyzed Intramolecular N-Arylation



The precursors to the quinoxalinone core were easily prepared from D,L-proline via the mixed anhydride protocol (Scheme 3) followed by Boc group deprotection. The resulting amine hydrochloride salts were obtained with sufficient purity (>95%) and were used for cyclization without further purification.

We then evaluated the intramolecular N-arylation reaction of a proline amide derivative (**9**) by using microwave irradiation. To start, we systematically evaluated a broad range of reaction

Scheme 3. Synthesis of Substituted Bromo Anilides as Precursors to Quinoxalinone Scaffolds



conditions, namely, the effects of altering catalyst, ligand, base, solvent, temperature, and reaction time on the percentage of conversion (Table 1). The two parameters we found to have the most significant impact on the cyclization were choice of solvent and base. The stronger bases such as *t*-BuOK, NaH, and LiHMDS were clearly superior to weaker bases such as Cs_2CO_3, DBU, and triethylamine (entries 1−8), and *t*-BuOK was found to be most efficient. Subsequent studies therefore utilized *t*-BuOK, and we varied only one parameter at a time. In terms of solvents, dioxane was found to be the best followed by DMA, DMF, and toluene (entries 10 vs 11 and 9 vs 12 and 13). $Pd(OAc)_2$ and $Pd_2(dba)_3$ were both effective catalysts for the cyclization, with $Pd_2(dba)_3$ affording slightly better conversions (entries 1, 2 vs 9, 10, respectively). Among 12 different ligands screened for cyclization (Figure 2), imidazoline carbene

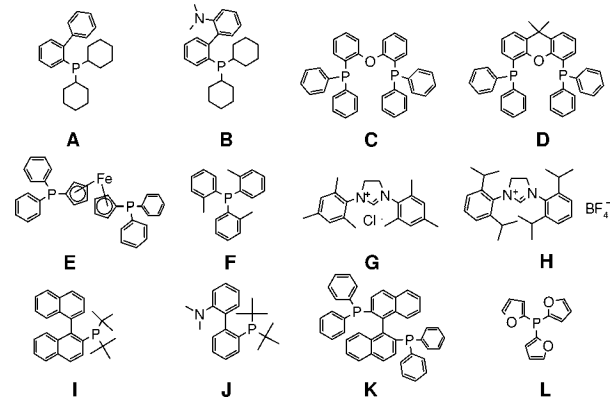


Figure 2. Ligand screening in Pd-catalyzed cyclization of compound **9**.

type ligands were found to be most effective. Ligand **H**, 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium tetrafluoroborate, led to the highest conversion (>95%) (Figure 3). The effects of varying catalyst or ligand loading on cyclization were found to be relatively small (Table 1, entries 14−20). Using 1 mol % of $Pd_2(dba)_3$ and 2 mol % of ligand **H** gave a quantitative conversion in just 10 min at 160 °C (entry 20). Overall, lower temperatures were found to be detrimental, but this could be compensated by prolonging the heating time in the microwave reactor, and the percentage of conversion could be improved up to 92% (entries 21−24). Control experiments showed that omitting the ligand afforded only 30% conversion, while no product was detected when both the catalyst and a ligand were left out (entries 25 and 26).

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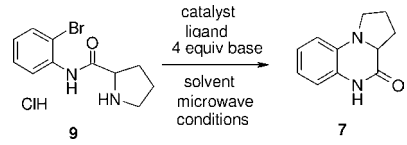
(8) For recent reviews, see: (a) Janey, J. M. In *Name Reactions for Functional Group Transformations*; Li, J. J., Corey, E. J., Eds.; Wiley-VCH: Weinheim, Germany, 2007; pp 564−609. (b) Appukkuttan, P.; Van der Eycken, E. *Eur. J. Org. Chem.* **2008**, 1133–1155.

(9) (a) Kirsch, G.; Hesse, S.; Comel, A. *Curr. Org. Synth.* **2004**, *1*, 47–63. (b) Ferraccioli, R.; Carenzi, D. *Synthesis* **2003**, 1383–1386. (c) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644–4680. (d) Mori, M.; Ishikura, M.; Ikeda, T.; Ban, Y. *Heterocycles* **1981**, *16*, 1491–1494. (e) Nishimura, Y.; Minamida, A.; Matsumoto, J.-i. *J. Heterocycl. Chem.* **1988**, *25*, 479–485. (f) Bower, J. F.; Szeto, P.; Gallagher, T. *Org. Lett.* **2007**, *9*, 3283–3286.

Table 1. Optimizing Cyclization: Studied Effect of Catalyst, Ligand, Base, Solvent, Reaction Time and Temperature on Conversion



9 7

entry	catalyst	ligand	base	solvent	conversion, %[a]
1	5 mol % $Pd(OAc)_2$	5 mol % C	*t*-BuOK	dioxane	64
2	5 mol % $Pd(OAc)_2$	5 mol % G	*t*-BuOK	dioxane	70
3	5 mol % $Pd(OAc)_2$	5 mol % C	Cs_2CO_3	dioxane	0
4	5 mol % $Pd(OAc)_2$	5 mol % G	Cs_2CO_3	dioxane	0
5	5 mol % $Pd_2(dba)_3$	5 mol % C	LiHMDS	dioxane	35
6	5 mol % $Pd_2(dba)_3$	5 mol % G	NaH	dioxane	46
7	5 mol % $Pd_2(dba)_3$	5 mol % G	DBU	dioxane	0
8	5 mol % $Pd_2(dba)_3$	5 mol % G	Et_3N	dioxane	0
9	5 mol % $Pd_2(dba)_3$	5 mol % C	*t*-BuOK	dioxane	72
10	5 mol % $Pd_2(dba)_3$	5 mol % G	*t*-BuOK	dioxane	80
11	5 mol % $Pd_2(dba)_3$	5 mol % G	*t*-BuOK	DMF	30
12	5 mol % $Pd_2(dba)_3$	5 mol % C	*t*-BuOK	DMA	50
13	5 mol % $Pd_2(dba)_3$	5 mol % C	*t*-BuOK	toluene	0
14	5 mol % $Pd_2(dba)_3$	5 mol % H	*t*-BuOK	dioxane	90
15	5 mol % $Pd_2(dba)_3$	10 mol % H	*t*-BuOK	dioxane	100
16	2 mol % $Pd_2(dba)_3$	2 mol % H	*t*-BuOK	dioxane	90
17	2 mol % $Pd_2(dba)_3$	4 mol % H	*t*-BuOK	dioxane	93
18	2 mol % $Pd_2(dba)_3$	6 mol % H	*t*-BuOK	dioxane	95
19	1 mol % $Pd_2(dba)_3$	1 mol % H	*t*-BuOK	dioxane	95
20	1 mol % $Pd_2(dba)_3$	2 mol % H	*t*-BuOK	dioxane	100
21	1 mol % $Pd_2(dba)_3$	2 mol % H	*t*-BuOK	dioxane	45[b]
22	1 mol % $Pd_2(dba)_3$	2 mol % H	*t*-BuOK	dioxane	75[c]
23	1 mol % $Pd_2(dba)_3$	2 mol % H	*t*-BuOK	dioxane	83[d]
24	1 mol % $Pd_2(dba)_3$	2 mol % H	*t*-BuOK	dioxane	92[e]
25	1 mol % $Pd_2(dba)_3$	none	*t*-BuOK	dioxane	30
26	none	none	*t*-BuOK	dioxane	0

[a] Conversions determined by LC/MS, not isolated; unless otherwise stated, reactions were run for 10 min at 160 °C in the microwave . [b] For 10 min at 120 °C. [c] For 20 min at 120 °C. [d] For 10 min at 140 °C. [e] For 20 min at 140 °C.

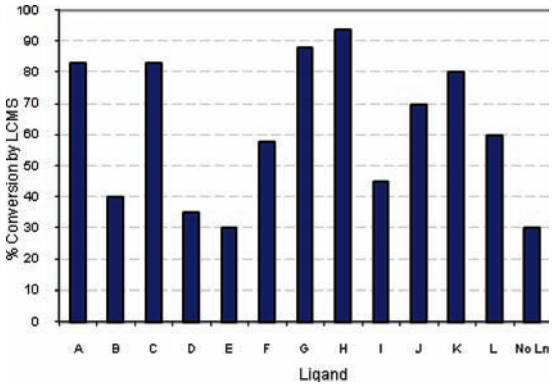
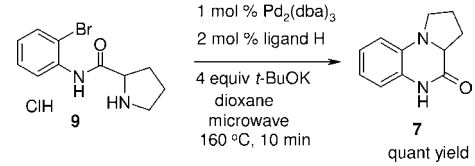


Figure 3. Ligand comparison in Pd-catalyzed cyclization of **9** by using 1 mol % of $Pd_2(dba)_3$ and 2 mol % of ligands. Reactions were run for 10 min at 160 °C in a microwave reactor.

On the basis of the above studies, the general reaction conditions require 1 mol % of $Pd_2(dba)_3$, 2 mol % of ligand **H**, and 4 equiv of *t*-BuOK. The mixture in dioxane is heated in a microwave reactor at 160 °C for 10 min (Scheme 4). The crude product can be typically purified by simply passing the crude reaction mixture through a short pad of silica gel.

Encouraged by our initial results, we sought to examine the scope and the generality of the method by exploring the effects of aryl substituents in bromoanilides on cyclization (Table 2). The general reaction conditions were used. Neutral (e.g., H-atom) and electron-donating groups on the benzene ring gave

Scheme 4. Optimized Conditions for the Synthesis of Quinoxalinone **7**



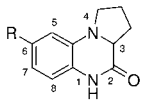
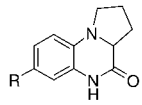
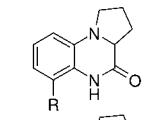
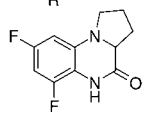
9 7
quant yield

very high conversions and isolated yields (>97%) (Table 2, entries 1−3 and 12). Likewise, electron-withdrawing groups at postion 7 afforded quantitative conversions (entries 10 and 11), suggesting these changes facilitated the cyclization. In contrast, electron-withdrawing groups at 6 and/or 8 positions were detrimental (entries 4−8 and 13,14), and no substantial improvement was found by switching to a different ligand (entries 13−15). Cyano-substituted substrate gave a quantitative conversion; however, the product seemed to be unstable and decomposition occurred during purification (entry 9).

Our general reaction conditions are also effective in preparing bicyclic scaffolds (Table 3, entries 1 and 2).

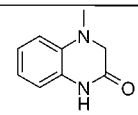
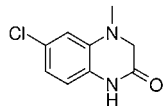
We next investigated the feasibility of extending the method to prepare more diverse quinoxalinones by varying cyclic amine precursors (Table 4). Using our general protocol, the cyclization was found to be efficient for secondary amines, such as azetidine, substituted pyrrolidines, and piperidine (entries 1, 2, 4, and 6). However, other amines

Table 2. Palladium-Catalyzed Cyclization: Substitution Effects

entry	product		conversion, %	isolated yield, % [c]
1		**7** R = H	100	quant
2		**10** R = i-Pr	100[a]	quant
3		**11** R = Me	100	97
4		**12** R = CF_3O	48[b]	—
5		**13** R = CF_3	31 (37[b])	—
6		**14** R = F	43 (49[b])	—
7		**15** R = Cl	42 (59[b])	43[b]
8		**16** R = Br	43[b]	—
9		**17** R = CN	100[b]	—[d]
10		**18** R = F	100	quant
11		**19** R = CF_3	100	quant
12		**20** R = Me	100	quant
13		**21** R = F	25	16
14		**22**	13	12

[a] Prolonged reaction time (30 min) needed for full conversion. [b] Ligand **G** was used instead. [c] Purified by passing through a short pad of silica gel. [d] Product decomposed.

Table 3. Synthesis of Bicyclic Quinoxalinones

entry	product		conversion, %	isolated yield, %
1		**30**	100	87[a]
2		**31**	85	81[b]

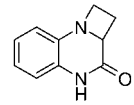
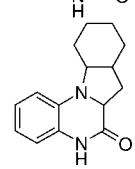
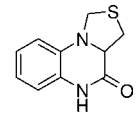
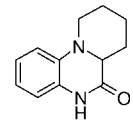
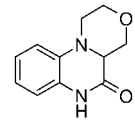
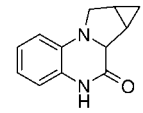
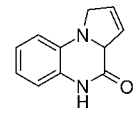
[a] Purified by passing through a short pad of silica gel. [b] Purified by flash chromatography with treated silica gel (2% triethylamine in dichloromethane).

such as thiazolidine, morpholine, and pyrroline only afforded <10% conversions (entries 3, 5, and 7).

Finally, we explored the possibility of running the reaction using conventional heating to prepare this scaffold on a large scale. Thus, the unsubstituted proline amide **9** in dioxane was refluxed in a flask with 1 mol % of $Pd_2(dba)_3$, 2 mol % of ligand **H**, and 4 equiv of *t*-BuOK under N_2 atmosphere. The cyclization went to completion after 16 h (Scheme 5). Quinoxalinone **7** was obtained on a gram scale in high yield (95%) after purified by passing through a short pad of silica gel.

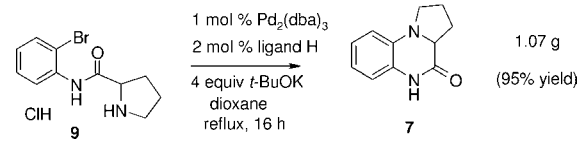
In summary, we have developed a practical and highly efficient route to pharmaceutically interesting bicyclic and polycyclic quinoxalinone scaffolds. This method enjoys relatively fast and clean reactions for a wide variety of bromoanilide

Table 4. Synthesis of Polycyclic Quinoxalinones

entry	product		conversion, %	isolated yield, % [a]
1		**23**	100	quant
2		**24**	100	quant
3		**25**	3	N/A
4		**26**	100	75
5		**27**	3	N/A
6		**28**	100	91
7		**29**	7	N/A

[a] Purified by passing through a short pad of silica gel.

Scheme 5. Synthesis of Quinoxalinone by Conventional Heating



substrates with easy purification. Moreover, the condition can be readily reproduced under conventional heating, which proves to be amenable for scaling up to gram quantity.

Acknowledgment. We gratefully acknowlwdge Drs. Sandrine Pache and Yun-Jin Hu (Department of Medicinal Chemistry, AstraZeneca R&D Montreal) for valuable discussions, Dr. Angelo Filosa and Mr. Pascal Turcotte (Department of Medicinal Chemistry, AstraZeneca R&D Montreal) for analytical supports.

Supporting Information Available: Experimental procedures and analytical data of all isolated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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