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Synthesis of Acridones by Palladium-Catalyzed Buchwald–Hartwig Amination

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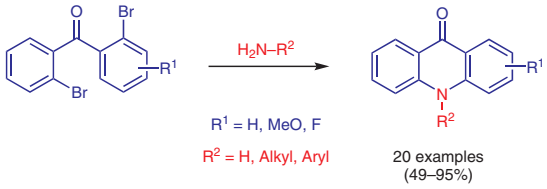

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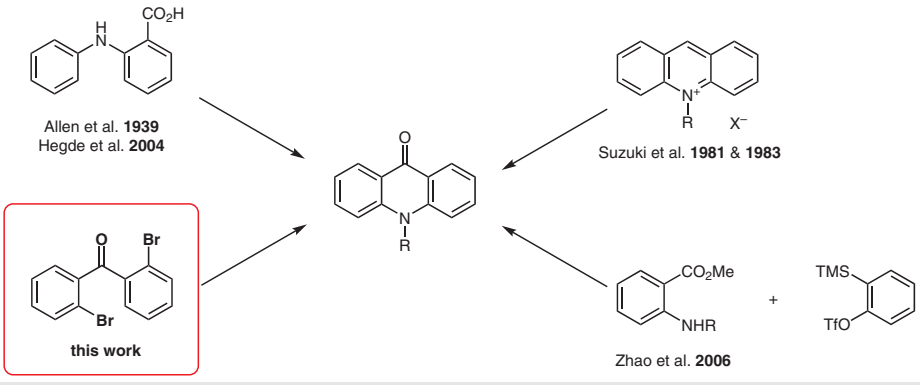
Abstract The Buchwald–Hartwig amination allows an efficient and convenient synthesis of biologically and pharmaceutically important acridones by formation of a six-membered ring. With the described method, a number of derivatives have been synthesized in up to 95% yield by using a variety of anilines as well as benzylic and aliphatic amines.

Key words palladium catalysis, Suzuki–Miyaura reaction, Buchwald–Hartwig amination, acridones, cyclization

Highly substituted acridones are versatile building blocks for many naturally occurring products. They have attracted attention of both medicinal and synthetic chemists because of to their various biological activities.[1–5] Acridone derivatives are promising antifungal and antiviral agents[2,4,5,6] as well as chemo-sensors and fluorescent labels in biodiagnostics.[1,6] With regard to DNA-intercalating anti-tumor agents,[2,4,5,7a,b,8] acridones are important precursors for the preparation of acridine derivatives with anti-cancer activities.[6] Classical routes to the synthesis of acridones rely on the acid-induced ring-closure of *N*-phenyl anthranilic acids, which are usually obtained from Ullmann condensation of anilines with *ortho*-halogen-substituted benzoic acids.[9] Furthermore, the oxidation of the corresponding acridinium salts by molecular oxygen under basic conditions[10] and the coupling of *ortho*-substituted anthranilic acid ester with arynes in the presence of CsF,[11] are known approaches (Scheme 1) as well as other methods.[2,5,6,8,12] However, harsh reaction conditions and tedious workup procedures are usually required.

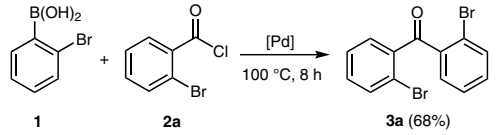
The two-fold Buchwald–Hartwig reaction has become a versatile tool for the construction of carbazoles and their heterocyclic isomers.[13] In contrast, the formation of six-or seven-memberered rings by this method has rarely been studied. The groups of Ando and Jensen studied the synthesis of Imipramine, a tricyclic antidepressant, containing a central azepine moiety.[14] More recently, Zhang et al. reported the synthesis of phenoxazines and phenothiazines by ring-closing two-fold Buchwald–Hartwig reactions.[15]



Scheme 1 Synthetic routes to acridones

In the present study, we report, to the best of our knowledge, a new and convenient synthesis of substituted acridones that is based on a double C–N amination, forming a six-membered ring (Scheme 1). This methodology is highly efficient, versatile and allows the introduction of various functional groups in good to excellent yields.

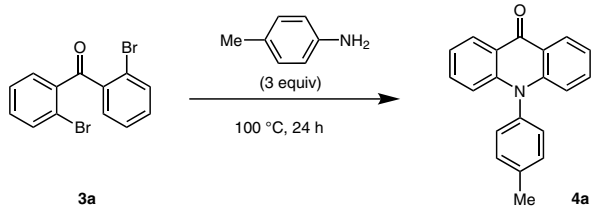
The starting material, 2,2'-dibromobenzophenone **3a**, was prepared by using a Suzuki–Miyaura reaction (Scheme 2). The desired product **3a** was isolated in a yield of 68%.



Scheme 2 Synthesis of precursor **3a**. *Reaction conditions*: $Pd(PPh_3)Cl_2$ (0.05 equiv, 0.03 mmol), K_3PO_4 (3 equiv, 2.05 mmol), 2-bromophenylboronic acid **1** (1.0 equiv, 0.68 mmol) and 2-bromobenzoyl chloride **2a** (1 equiv, 0.68 mmol), toluene

Then, the palladium-catalyzed Buchwald–Hartwig amination of **3a** with different anilines was studied (Table 1) and the influence of different ligands and solvents was examined. To our satisfaction, an initial test reaction with use of $PtBu_3{\cdot}HBF_4$ and toluene gave the desired product **4a** in 17% yield (Table 1, entry 1). Next, we screened several phosphorus ligands under otherwise identical conditions (Table 1, entry 2–4). It turned out that the employment of the bidentate phosphorus ligand dppf and toluene at 100 °C for 24 hours proved to be the most efficient combination, with the desired product **4a** being isolated in up to 95% yield.[16] Surprisingly, the use of xylene at 140 °C led to significantly lower yields (Table 1, entry 6).

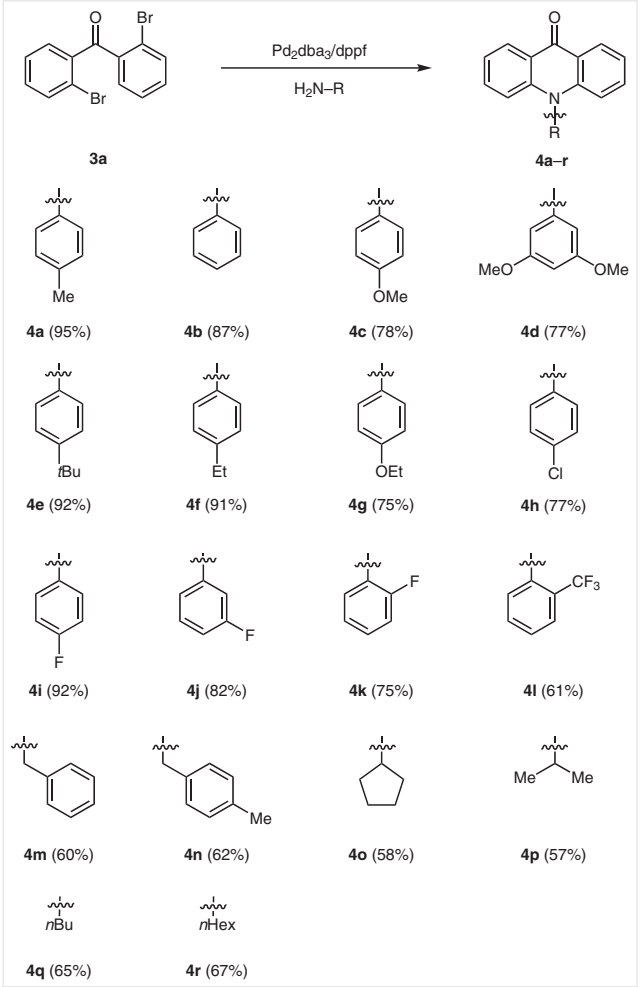
Table 1 Optimization of the Preparation of **4a**[a,b]



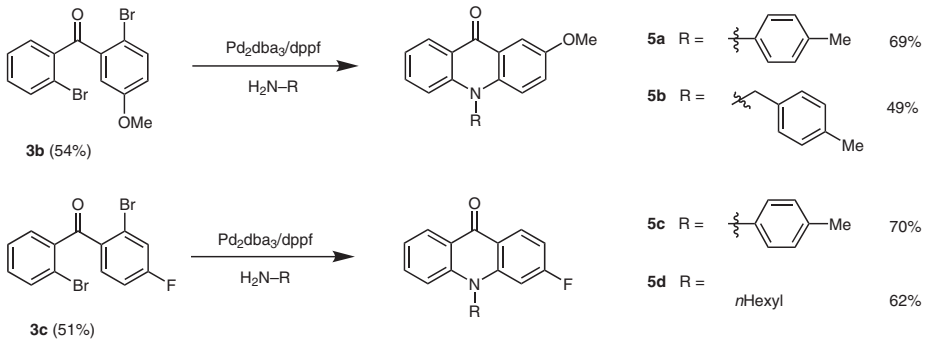
Entry	Ligand	Solvent	Temp (°C)	Yield (%)[b]
1	$PtBu_3{\cdot}HBF_4$	toluene	100	17
2	BINAP	toluene	100	12
3	X-Phos	toluene	100	17
4	**dppf**	**toluene**	**100**	**95**
5	dppf	1,4-dioxane	90	37
6	dppf	xylene	140	39

[a] *Reaction conditions*: **3a** (1.0 equiv, 0.3 mmol), Pd_2dba_3 (0.05 equiv, 0.015 mmol), *p*-toluidine (3.0 equiv, 0.9 mmol) and ligand (monodentate $PtBu_3{\cdot}HBF_4$ or X-Phos 0.2 equiv; bidentate BINAP or dppf 0.1 equiv), KO*t*Bu (6.0 equiv, 1.8 mmol), solvent (3.0 ml).
[b] Isolated yields.

Having the optimized reaction conditions in hand, we carried out Buchwald–Hartwig reactions of compounds **4a–r** containing various functional groups (Scheme 3). The yields for the double C–N coupling reaction vary from moderate to excellent. With regard to the substitution pattern of the anilines employed, electron-withdrawing and electron-donating groups both proved to be compatible with the reaction conditions and gave equally good results. The highest yield was observed for **4a** (95%), whereas the lowest occurred with **4l** with a CF_3 group attached at the *ortho* position of the aniline (61%). In particular, the impact of steric hindrance on the aromatic moiety was investigated. The yields decrease gradually from *para*-substituted compound **4i** (92%) to *ortho*-substituted compounds **4k** (75%) and **4l** (61%). Furthermore, we found that the reaction conditions could be successfully applied to various benzylic and aliphatic amines, giving acridinones **4m–r** in slightly lower yields of up to 67%.



Scheme 3 Synthesis of acridones **4a–r**. *Reaction conditions*: **3a** (1.0 equiv, 0.3 mmol), Pd_2dba_3 (0.05 equiv, 0.015 mmol), amine (3.0 equiv); dppf (0.1 equiv), KO*t*Bu (6.0 equiv), toluene, 100 °C, 24 h. Isolated yields are given in parenthesis.



Scheme 4 Synthesis of **5a–d**

Next, we turned our attention to the employment of substituted 2,2'-dibromobenzophenones. As examples, we chose benzophenones that contained an electron-donating methoxy group (**3b**) and an electron-withdrawing fluorine functionality (**3c**). The starting materials **3b**,**c** were prepared according to the conditions of the Suzuki–Miyaura reaction mentioned above. However, isolated compounds **3b** (54%) and **3c** (51%) were accompanied by low amounts of diarylated side products **6b**,**c**, derived from arylation of the bromine of the aryl chloride.[17] Fortunately, such side products did not affect the following cyclizations and, hence, slightly contaminated products **3b** and **3c** were used as isolated. The reaction with *p*-toluidine gave equally good yields of about 70% for **5a** and **5c** from starting materials **3b** and **3c**, respectively. However, yields decreased slightly with an aromatic *N*-substituted compound **5a** (69%) and **5c** (70%) to an aliphatic **5d** (62%) and a benzylic *N*-substituted compound **3b** (49%) (Scheme 4).

In conclusion, we have developed a simple and convenient synthetic pathway for the preparation of acridones by formation of a six-membered ring by a palladium-catalyzed Buchwald–Hartwig amination. The optimized reaction conditions allow the modular synthesis of various functionalized acridones and tolerate a range of functional groups on the aryl rings as well as the employment of anilines, benzylic and aliphatic amines, leading to the corresponding products in good to very good yields.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1612256.

References and Notes

(1) Del Buttero, P.; Gironda, R.; Moret, M.; Papagni, A.; Parravicini, M.; Rizzato, S.; Miozzo, L. *Eur. J. Org. Chem.* **2011**, 2265.
(2) Huang, P.-C.; Parthasarathy, K.; Cheng, C.-H. *Chem. Eur. J.* **2013**, *19*, 460.
(3) Kobayashi, K.; Nakagawa, K.; Yuba, S.; Komatsu, T. *Helv. Chim. Acta* **2013**, *96*, 389.
(4) Pal, C.; Kundu, M. K.; Bandyopadhyay, U.; Adhikari, S. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3563.
(5) Zhao, J.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 583.
(6) Nishio, R.; Wessely, S.; Sugiura, M.; Kobayashi, S. *J. Comb. Chem.* **2006**, *8*, 459.
(7) (a) Mayur, Y. C.; Peters, G. J.; Lemos, C.; Kathmann, I.; Prasad, V. V. S. R. *Arch. Pharm.* **2009**, *342*, 640. (b) Sathish, N. K.; GopKumar, P.; Prasad, V. V. S. R.; Kumar, S. M. S.; Mayur, Y. C. *Med. Chem. Res.* **2010**, *19*, 674.
(8) Singh, P.; Kaur, J.; Yadav, B.; Komath, S. S. *Bioorg. Med. Chem.* **2009**, *17*, 3973.
(9) (a) Hegde, R.; Thimmaiah, P.; Yerigeri, M. C.; Krishnegowda, G.; Thimmaiah, G. N.; Houghton, P. J. *Eur. J. Med. Chem.* **2004**, *39*, 161. (b) Allen, C. F. H. *McKee G. H. W.* **1939**, *19*, 6.
(10) (a) Suzuki, N.; Kazui, Y.; Kato, M.; Izawa, Y. *Heterocycles* **1981**, *16*, 2121. (b) Suzuki, N.; Kazui, Y.; Tsukamoto, T.; Kato, M.; Izawa, Y. *Bull. Chem. Soc. Jpn.* **1983**, 1519.
(11) Zhao, J.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 583.
(12) (a) Dubrovskiy, A. V.; Larock, R. C. *J. Org. Chem.* **2012**, *77*, 11232. (b) Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 168.
(13) (a) Hoang, H. D.; Janke, J.; Amirjanyan, A.; Ghochikyan, T.; Flader, A.; Villinger, A.; Ehlers, P.; Lochbrunner, S.; Surkus, A.-E.; Langer, P. *Org. Biomol. Chem.* **2018**, *16*, 6543. (b) Pham, N. N.; Janke, S.; Salman, G. A.; Dang, T. T.; Le, T. S.; Spannenberg, A.; Ehlers, P.; Langer, P. *Eur. J. Org. Chem.* **2017**, 5554. (c) Ohlendorf, L.; Diaz Velandia, J. E.; Konya, K.; Ehlers, P.; Villinger, A.; Langer, P. *Adv. Synth. Catal.* **2017**, *359*, 1758. (d) Kitawaki, T.; Hayashi, Y.; Chida, N. *Heterocycles* **2005**, *65*, 1561. (e) Nozaki, K.; Takahashi, K.; Nakano, K.; Hiyama, T.; Tang, H.-Z.; Fujiki, M.; Yamaguchi, S.; Tamao, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 2051.
(14) (a) Christensen, H.; Schjoth-Eskesen, C.; Jensen, M.; Sinning, S.; Jensen, H. H. *Chem. Eur. J.* **2011**, *17*, 10618. (b) Sato, K.; Inoue, Y.; Mori, T.; Sakaue, A.; Tarui, A.; Omote, M.; Kumadaki, I.; Ando, A. *Org. Lett.* **2014**, *16*, 3756.
(15) (a) Zhang, L.; Huang, X.; Zhen, S.; Zhao, J.; Li, H.; Yuan, B.; Yang, G. *Org. Biomol. Chem.* **2017**, *15*, 6306. (b) Zhang, X.; Yang, Y.; Liang, Y. *Tetrahedron Lett.* **2012**, *53*, 6406.
(16) **Typical Procedure – Synthesis of 10-(4-Methylphenyl)-acridin-9(10*H*)-one (4a)**
A dried glass pressure tube under argon was charged with 2,2'-dibromobenzophenone **3a** (100 mg, 0.3 mmol), Pd_2dba_3 (14 mg, 0.015 mmol), dppf (16 mg, 0.03 mmol), KO*t*Bu (200 mg, 1.8 mmol), and amine (0.1 ml, 0.9 mmol). The solids were dissolved in dry toluene (3 mL), sealed with a Teflon® cap before being heated to 100 °C. After 24 h, the mixture was allowed to cool to room temperature. The residue was dissolved in CH_2Cl_2 (20 mL), washed with hydrochloric acid (1 M, 20 mL) and dried

with Na_2SO_4. After filtration and removal of the solvents under reduced pressure, the crude solid was purified by column chromatography (heptane/ethyl acetate 10:1) to give 10-(4-methylphenyl)acridin-9(10*H*)-one (**4a**) as a yellow solid (80 mg, 95%), mp 290–292 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.58 (dd, ^3J = 8.0 Hz, ^4J = 2.1 Hz, 2 H, CH_{Ar}), 7.53–7.45 (m, 4 H, CH_{Ar}), 7.30–7.21 (m, 4 H, CH_{Ar}), 6.80 (d, ^3J = 9.0 Hz, 2 H, CH_{Ar}), 2.54 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.2 (CO), 143.3 (2 C_{Ar}), 139.8 (C_{Ar}), 136.3 (C_{Ar}), 133.3 (2 CH_{Ar}), 131.8 (2 CH_{Ar}), 129.7 (2 CH_{Ar}), 127.3 (2 CH_{Ar}), 121.9 (2 C_{Ar}), 121.5 (2 CH_{Ar}), 117.0 (2 CH_{Ar}), 21.4 (CH_3). IR (ATR, cm^{-1}): 3033 (w), 2921 (w), 2853 (w), 1630 (m), 1596 (m), 1485 (m), 1456 (m), 1299 (m), 1271 (m), 1156 (m), 1038 (m), 1025 (m), 935 (m), 824 (m), 753 (s), 673 (m), 520 (m). MS (EI, 70 eV): *m/z* (%) = 286 (20), 285 ([M]$^+$, 100), 284 (12), 241 (15), 166 (11), 140 (17), 139 (10), 91 (12), 89 (13), 77 (12), 76 (13), 65 (22), 63 (15), 50 (11), 39 (15). HRMS (EI): *m/z* [M]$^+$ calcd for $C_{20}H_{15}O_1N_1$: 285.11482; found: 285.11482.

(17) Gao, Q.; Xu, S. *Org. Biomol. Chem.* **2018**, *16*, 208.