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Two-Step Total Syntheses of Canthin-6-one Alkaloids: New One-Pot Sequential Pd-Catalyzed Suzuki−Miyaura Coupling and Cu-Catalyzed Amidation Reaction

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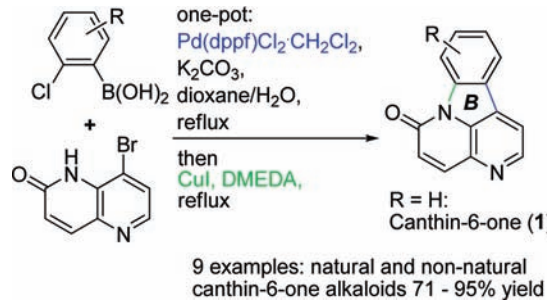
ABSTRACT



Canthin-6-one (1) and nine analogues including the naturally occurring 9-methoxycanthin-6-one (2) and amaroridine (3) are prepared rapidly and in high yields via a convergent "non-classical" strategy that focuses on construction of the central ring *B*. The strategy relies on concomitant Pd-catalyzed Suzuki−Miyaura C−C coupling followed by a Cu-catalyzed C−N coupling that can be achieved either stepwise or in a new one-pot protocol starting from the appropriate 8-bromo-1,5-naphthyridine.

Canthinones are β-carboline alkaloids that have an additional ring fusion affording a tetracyclic core (Figure 1). Canthinone **1**, first isolated by Haynes in 1952,[1] has a promising biological profile;[1b,2] as such, its synthesis has generated significant interest. Over 40 natural occurring analogues have now been reported,[1b,2] e.g., 9-methoxycanthin-6-one (**2**),[3] amaroridine (**3**),[4] or the more complex curtisin (**4**).[5]

The known reported syntheses of canthinones[6] all start from either indoles or tryptophans. The retrosynthesis of canthinone to afford indole synthons could therefore be considered as "classical". We required a convergent and flexible synthesis that was suitable for the rapid generation of a diverse compound library for biological studies. In light

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[‡] Cyano Research Corporation Ltd.

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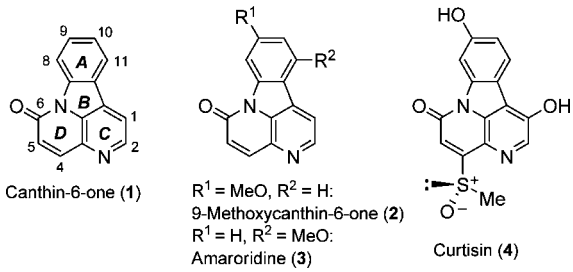
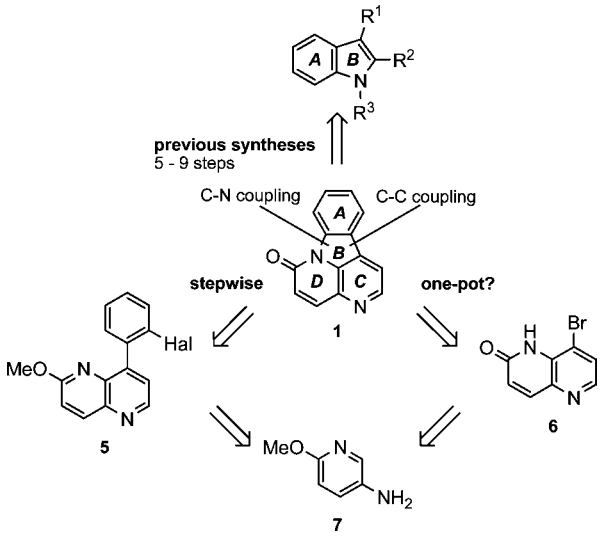


Figure 1. Structure and chemical numbering of canthin-6-one (**1**) and selected examples from over 40 natural analogues.

of this, we reevaluated the retrosynthesis of canthinone **1** and identified a nonclassical route that revolved around constructing ring *B* via transition-metal C−C and C−N coupling chemistry.

Adding the *A* ring at the end of the synthesis can introduce flexibility for modifying the C8−C11 positions (Scheme 1).

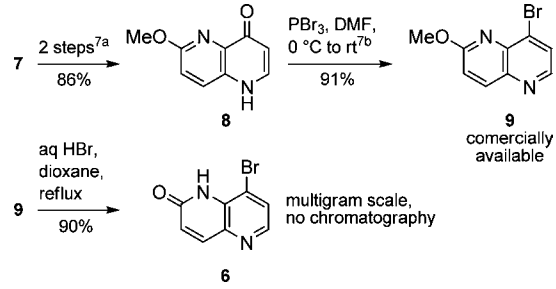
Scheme 1. Retrosynthetic Analysis of Canthin-6-one (**1**)



This could be achieved by an intermolecular C−C coupling followed by an intramolecular C−N coupling, either via a stepwise or a one-pot procedure. The stratergy required access to 1,5-naphthyridines **5** and **6**, which can be prepared from cheap 6-methoxypyridin-3-amine (**7**).

The aminopyridine **7** was converted into comercially available 8-bromo-2-methoxy-1,5-naphthyridine (**9**) in three steps (Scheme 2).[7] Demethylation using aqueous HBr in dioxane gave the key precursor 8-bromo-1,5-naphthyrid-2(1*H*)-one (**6**) that can be prepared in multigram batches (5 g).

Scheme 2. Preperation of Key Naphthyridines **6** and **9**



For the stepwise approach, the desired 8-(2-chlorophenyl)-2-methoxynaphthyridine **10** was prepared from 8-bromo-2-methoxynaphthyridine **9** and 2-chlorophenylboronic acid via a Suzuki−Miyaura coupling. Initial efforts using either $Pd(Ph_3P)_4$ or $Pd(OAc)_2$ in aqueous dioxane and K_2CO_3 suffered from formation of either significant amounts of biphenyls or protodehalogenation of the naphthyridine, respectively. The latter problem could be resolved with the use of anhydrous toluene as solvent. After additional efforts, the reaction proceeded in excellent yield when $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ was used together with K_2CO_3 in a dioxane/H_2O solvent system (Table 1, entry 1). Refluxing the 8-aryl-2-methoxynaphthyridine **10** with aqueous HCl in dioxane gave the naphthyridone **11** in 90% yield. On completion (by TLC) of the Suzuki−Miyaura reaction, the direct addition of aqueous HCl to the mixture followed by 1 h at reflux allowed both steps to be achieved in one-pot. To our delight, the final C−N coupling worked using Buchwald's conditions,[8] [CuI (5 mol %), DMEDA (10 mol

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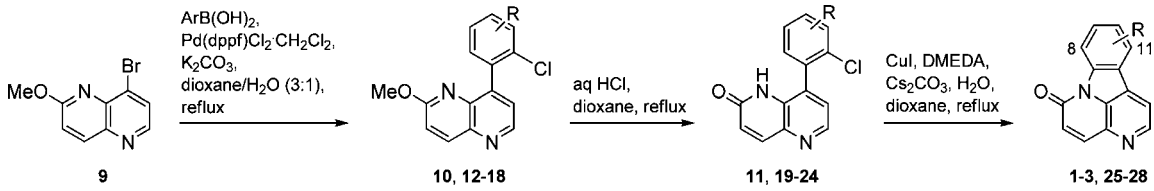
Table 1. Stepwise Synthesis of Canthin-6-one Alkaloids via 8-Bromonaphthyridine **9**



entry	$ArB(OH)_2$	yields (%)	yields (%)[c]/yields one-pot (%)	yields (%)
1	$2\text{-ClC}_6H_4B(OH)_2$	**10** R = H (98)[a]	**11** R = H (90)/(90)[d]	**1** R = H (99)[f]
2	$2,3\text{-Cl}_2C_6H_3B(OH)_2$	**12** R = Cl (93)[b]	**19** R = Cl (84)	**25** R = Cl (94)[g]
3	$2,4\text{-Cl}_2C_6H_3B(OH)_2$	**13** R = Cl (93)[b]	**20** R = Cl (89)	**26** R = Cl (98)[g]
4	$2\text{-Cl-4-MeOC}_6H_3B(OH)_2$	**14** R = MeO (88)[b]	**21** R = MeO (85)/(80)[e]	**2** R = MeO (97)[g]
5	$2,5\text{-Cl}_2C_6H_3B(OH)_2$	**15** R = Cl (88)[b]	**22** R = Cl (85)	**27** R = Cl (96)[g]
6	$2\text{-Cl-5-F}_3CC_6H_3B(OH)_2$	**16** R = F_3C (90)[b]	**23** R = F_3C (94)/(89)[e]	**28** R = F_3C (98)[g]
7	$2,6\text{-Cl}_2C_6H_3B(OH)_2$	**17** R = Cl (mixture)[b]		
8	$2\text{-Cl-6-MeOC}_6H_3B(OH)_2$	**18** R = MeO (85)[b]	**24** R = MeO (94)/(82)[e]	**3** R = MeO (91)[g]

[a] Reagents and conditions: $ArB(OH)_2$ (1.2 equiv), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (2 mol %), K_2CO_3 (2 equiv), dioxane/H_2O (3:1), reflux. [b] Reagents and conditions: $ArB(OH)_2$ (1.5 equiv), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (4 mol %), K_2CO_3 (2 equiv), dioxane/H_2O (3:1), reflux. [c] Reagents and conditions: HCl concd, H_2O, dioxane. [d] Reagents and conditions: $ArB(OH)_2$ (1.2 equiv), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (2 mol %), K_2CO_3 (2 equiv), dioxane/H_2O (3:1), reflux, then HCl, reflux. [e] Reagents and conditions: $ArB(OH)_2$ (1.5 equiv), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (5 mol %), K_2CO_3 (2 equiv), dioxane/H_2O (3:1), reflux, then HCl, reflux. [f] Reagents and conditions: CuI (5 mol %), DMEDA (10 mol %), Cs_2CO_3 (2 equiv), H_2O (2 equiv), dioxane, reflux. [g] Reagents and conditions: CuI (10 mol %), DMEDA (20 mol %), Cs_2CO_3 (2 equiv), H_2O (2 equiv), dioxane, reflux.

%) as ligand, and H_2O (2 equiv) in dioxane at reflux], in only 15 min and in 99% yield. The first approach, therefore, gave canthinone **1** in only five steps and in 70% overall yield starting from aminopyridine **7**.

Since there are a wide variety of 2-chlorophenylboronic acids,[9] we prepared several canthinone analogues in a similar manner (Table 1, column 1). 2,3-, 2,4-, and 2,5-disubstituted phenylboronic acids reacted smoothly to give arylnaphthyridines **12**−**16**. Even the sterically demanding 2-chloro-6-methoxyphenylboronic acid gave the analogue **18** in good yield. 2,6-Dichlorophenylboronic acid, however, gave a mixture of the 8-arylnaphthyridine **17** and mainly unreacted starting material, which was difficult to separate. The subsequent demethylations (Table 1, column 2) could be performed using HCl in good yields for arylnaphthyridones **19**−**24**.

The one-pot coupling/demethylation method was unfavorable for the 8-dichlorophenylnaphthyridones **19**, **20**, and **22**, which partly suffered protodehalogenation.

Finally, the C−N coupling using CuI (10 mol %) and DMEDA (20 mol %)[8] gave six new canthinone alkaloids **2**, **3**, and **25**−**28** in good overall yields (Table 1, column 3). 9-Methoxycanthin-6-one (**2**)[3] and 11-methoxycanthin-6-one (amaroridine, **3**)[4] represent natural products that to our knowledge have not been previously synthesized.

In an effort to further simplify the synthesis, we targeted an ambitious one-pot protocol for canthinones from 8-bromo-1,5-naphthyridone **6**. A variety of nitrogen heterocycles have been prepared using domino, tandem, or one-pot transition-metal-catalyzed coupling procedures.[10] However, very few sequential transition-metal-catalyzed coupling reactions are known that use two different catalyst systems in the same pot since many transformations are catalyst and/or ligand specific.[11] Combining such protocols can greatly facilitate the rapid preparation of compound libraries.

Satisfied with the Suzuki−Miyaura coupling of the bromonaphthyridine **9**, we initially applied the same conditions

(9) Seventy-seven substituted 2-chlorophenylboronic acids are comercially available (SciFinder 11 January, 2010).

(10) For recent examples, see: (a) Candito, D. A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6713. (b) Fayol, A.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 4203. (c) Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2005**, *7*, 3449. (d) Furuta, T.; Kitamura, Y.; Hahimoto, A.; Fujii, S.; Tanaka, K.; Kan, T. *Org. Lett.* **2007**, *9*, 183. (e) Kitamura, Y.; Yashikawa, S.; Furuta, T.; Kan, T. *Synlett* **2008**, 377. (f) Ferraccioli, R.; Carenzi, D.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.* **2006**, *128*, 722. (g) Ferraccioli, R.; Carenzi, D.; Rombolà, O.; Catellani, M. *Org. Lett.* **2004**, *6*, 4759.

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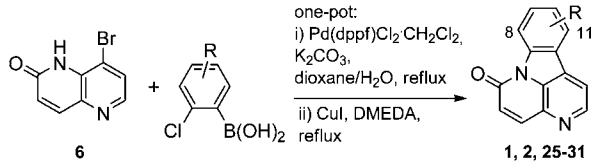
Table 2. One-Pot Synthesis of Canthin-6-ones



entry	$ArB(OH)_2$	yields (%)
1[a]	2-$ClC_6H_4B(OH)_2$	**1** R = H (95)
2[b]	2,3-$Cl_2C_6H_3B(OH)_2$	**25** R = Cl (82)
3[a]	2-Cl-4-$MeC_6H_4B(OH)_2$	**29** R = Me (92)
4[b]	2,4-$Cl_2C_6H_3B(OH)_2$	**26** R = Cl (82)
5[b]	2-Cl-4-$FC_6H_3B(OH)_2$	**30** R = F (88)
6[b]	2-Cl-4-$F_3CC_6H_3B(OH)_2$	**31** R = F_3C (78)
7[b]	2-Cl-4-$MeOC_6H_3B(OH)_2$	**2** R = MeO (92)
8[b]	2,5-$Cl_2C_6H_3B(OH)_2$	**27** R = Cl (77)
9[b]	2-Cl-5-$F_3CC_6H_3B(OH)_2$	**28** R = F_3C (71)[c]
10[b]	2,6-$Cl_2C_6H_3B(OH)_2$	R = Cl (0)[d]
11[b]	2-Cl-6-$MeOC_6H_3B(OH)_2$	**3** R = MeO (trace)[d]

[a] Reagents and conditions: (i) $Pd(dppf)Cl_2.CH_2Cl_2$ (2 mol %), $ArB(OH)_2$ (1.1 equiv), K_2CO_3 (3 equiv), dioxane/H_2O (3:1), 0.5 h; (ii) CuI (5 mol %), DMEDA (10 mol %), dioxane/H_2O (3:1), 15 min. [b] Reagents and conditions: (i) $Pd(dppf)Cl_2$·CH_2Cl_2 (5 mol %), $ArB(OH)_2$ (2 equiv), K_2CO_3 (3 equiv), dioxane/H_2O (3:1), 80 min; (ii) CuI (10 mol %), DMEDA (20 mol %), dioxane/H_2O (3:1), 40 min. [c] Recovery of naphthyridone **6** (12%). [d] Recovery of naphthyridone **6** (80%).

to the reaction of 8-bromo-1,5-naphthyridone **6** and 2-chlorophenylboronic acid and obtained 8-(2-chlorophenyl)naphthyrid-2(1*H*)-one **11** in high yield. Our initial hopes that the final C−N coupling would be catalyzed by the already present Pd species did not materialize. Nevertheless, on completion of the Suzuki−Miyaura reaction (by TLC), the addition to the refluxing mixture of a preformed deep blue complex of CuI (5 mol %) and DMEDA (10 mol %) in dioxane gave in only 20 min canthinone **1** in near-quantitative yield (Table 2).[12] The one-pot protocol was successfully applied to other 2-chlorophenylboronic acids: 2-Chloro-4-methylphenylboronic acid gave excellent yields of canthinone **29** (Table 2, entry 3), while reactions with less activated 2,3-, 2,4-, and 2,5-disubstituted phenylboronic acids gave good conversions and yields when 2 equiv of arylboronic acids and higher catalyst loadings were used (Table 2, entries 2 and 4−9). With the sterically demanding 2,6-disubstituted phenylboronic acids the C−C coupling did not work, preventing access to the 11-substituted canthinones via this route. Using this new one-pot protocol, we produced nine canthinones **1**, **2**, and **25**−**31** sporting various substituents on the *A* ring quickly and in excellent yields of 71−95% (Table 2).

(12) The simultaneous addition of both the Pd and Cu catalysts at the start of the reaction gave mainly recovered naphthyridone **6**. More information can be found in the Supporting Information.

In conclusion, two high-yielding and flexible syntheses of canthin-6-one (**1**) were developed and optimized. The first provided a five-step synthesis of canthinone **1** in an overall yield of over 70% via cheap 6-methoxypyridin-3-amine (**7**) and in only two steps from comercially available precursor 8-bromo-2-methoxynaphthyridine **9** (89%). The second was a simple and useful one-pot protocol that involved a sequential application of a Pd-catalyzed Suzuki−Miyaura coupling followed by a Cu-catalyzed amidation that could be of general use for synthetic chemists. In total, 10 canthinones including the first syntheses of naturally occuing 9-methoxycanthin-6-one (**2**) and amaroridine (**3**) were reported.

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

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