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INDOLOQUINONES, PART 8.[1] PALLADIUM(II)-CATALYZED TOTAL SYNTHESIS OF MURRAYAQUINONE A, KOENIGINEQUINONE A, AND KOENIGINEQUINONE B

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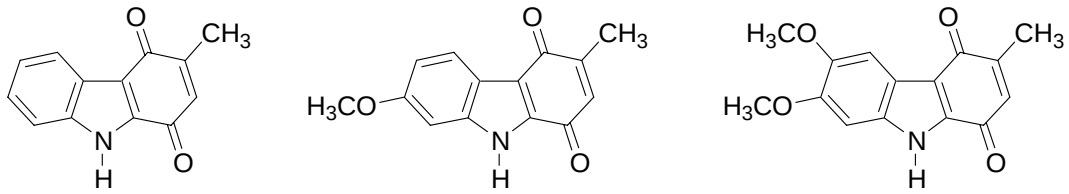
Abstract – Regioselective addition of the appropriate arylamines to 2-methyl-1,4-benzoquinone followed by a palladium(II)-catalyzed oxidative cyclization opens up an efficient route to the naturally occurring 3-methylcarbazole-1,4-quinone alkaloids murrayaquinone A, koeniginequinone A, and koeniginequinone B.

Numerous carbazole alkaloids with interesting structural features and useful pharmacological activities have been isolated from different natural sources over the past four decades.[1,2] Because of the strong interest in these natural products several new methodologies directed towards their total synthesis were developed.[1-3] The first carbazole-1,4-quinone alkaloids were isolated only 20 years ago by Furukawa.[4] Murrayaquinone A (**1**) was isolated from the root bark of *Murraya euchrestifolia* (Scheme 1).[5] Since then, many naturally occurring carbazole-1,4-quinone alkaloids have been found.[6] In 1998, Chowdhury isolated koeniginequinone A (**2**) and koeniginequinone B (**3**) from the stem bark of *Murraya koenigii*.[7] Murrayaquinone A (**1**) shows cardiotonic activity.[8] The pharmacological potential of the carbazole-1,4-quinone alkaloids induced the development of diverse synthetic approaches to these natural products.[6,9]

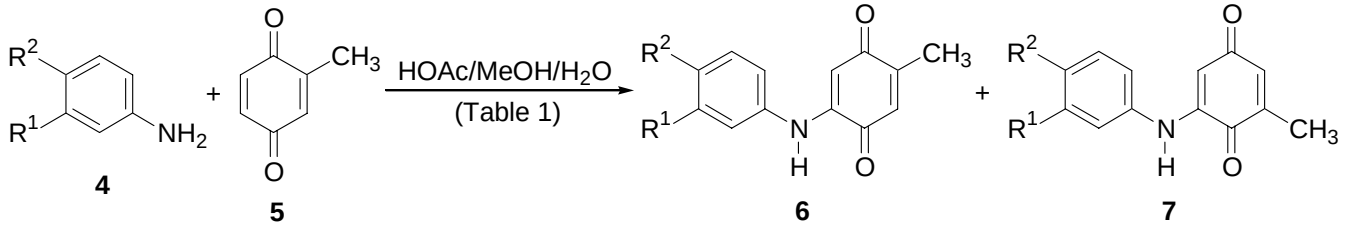


1 Murrayaquinone A **2** Koeniginequinone A **3** Koeniginequinone B

Scheme 1

We described the iron-mediated construction of the carbazole framework by consecutive C–C and C–N bond formation.[3c,g,h] This method was applied to the total synthesis of murrayaquinone A (**1**),[10] and the carbazole-1,4-quinol alkaloids carbazomycin G and H.[11] An alternative approach with a reversed sequence of bond formations generates the carbazole nucleus by a palladium(II)-catalyzed oxidative C–C bond formation of appropriately substituted arylamino-1,4-benzoquinones as key-step. The second method was used for the synthesis of benzo[*b*]carbazole-6,11-quinones (representing benzo[*b*]-annulated carbazole-1,4-quinones),[12] carbazomycin G and H,[13] and the carbazole-3,4-quinone alkaloid carbazoquinocin C.[1,14] We now describe the palladium(II)-catalyzed total synthesis of the 3-methyl-carbazole-1,4-quinone alkaloids (**1**-**3**) using our second approach.

The first step in our palladium(II)-catalyzed total synthesis of carbazomycin G and H and carbazoquinocin C was the addition of the arylamine to 2-methoxy-3-methyl-1,4-benzoquinone, which provided regioselectively the desired 5-arylamino-2-methoxy-3-methyl-1,4-benzoquinone in more than 80% yield.[1,13,14] In the present case, starting from 2-methyl-1,4-benzoquinone, the corresponding step was more difficult because of the expected regioselectivity problem.[15]



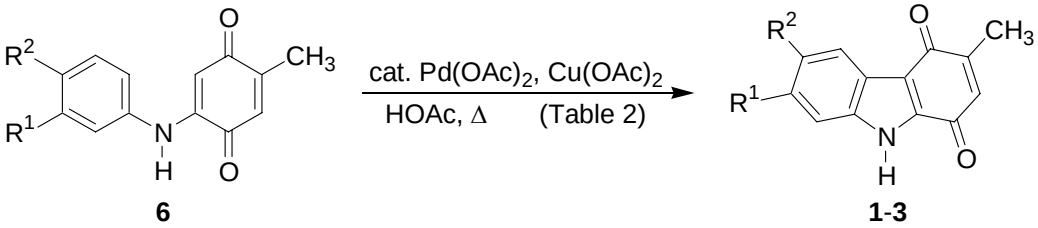
Scheme 2

Table 1. Addition of the arylamines (**4**) to 2-methyl-1,4-benzoquinone (**5**)

4	R^1	R^2	*T* (°C)	*t* (d)	**6**/**7**, Yield (%)	**6**/**7**, Ratio
a	H	H	– 4	4	100	2.3 : 1
b	OCH_3	H	– 4	5	88	2.9 : 1
c	OCH_3	OCH_3	– 2	4	90	2.5 : 1

Using standard conditions,[1,16] reaction of the arylamines (**4**) with 2-methyl-1,4-benzoquinone (**5**) in methanol at room temperature for a few hours, afforded the 5-arylamino-2-methyl-1,4-benzoquinones (**6**) in only 20-30% yield along with the 6-arylamino-2-methyl-1,4-benzoquinones (**7**) as by-products. We then applied the procedure reported by Musso,[17] addition of a solution of the arylamine (**4**) in 5% acetic acid to a solution of 2-methyl-1,4-benzoquinone (**5**) in methanol/water at low temperature and subsequent reaction for a few days (ratio, 5% HOAc : MeOH : H_2O = 1 : 5 : 15). Using these reaction conditions, the addition products were obtained in 88-100% yield and in ratios ranging from 2.3-2.9 to 1 in favor of the desired 5-arylamino-2-methyl-1,4-benzoquinones (**6**) (Scheme 2, Table 1). The regioisomers (**6**) and (**7**) were separated by flash chromatography on silica gel using hexane/ethyl acetate as eluent.

Furukawa described the first palladium(II)-mediated oxidative cyclization of 2-anilino-1,4-benzoquinones to carbazole-1,4-quinones.[18] In the synthesis of benzo[*b*]carbazole-6,11-diones, we demonstrated that this reaction becomes catalytic in palladium by reoxidation of Pd(0) to Pd(II) with Cu(II).[12,19] Åkermark subsequently reported a palladium(II)-catalyzed cyclization of 2-anilino-1,4-benzoquinones by reoxidation of Pd(0) with *tert*-butyl hydroperoxide.[20] We applied our procedure to the total syntheses of the carbazole-1,4-quinol alkaloids carbazomycin G and H[13] and the carbazole-3,4-quinone alkaloid carbazoquinocin C.[1,14] We now describe the oxidative cyclization of the 5-arylamino-2-methyl-1,4-benzoquinones (**6**) to the 3-methylcarbazole-1,4-quinone alkaloids (**1**-**3**) (Scheme 3, Table 2).

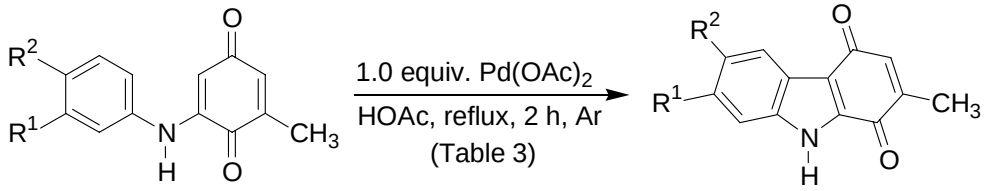


Scheme 3

Table 2. Results of the oxidative cyclization of the 5-arylamino-2-methyl-1,4-benzoquinones (**6**)

6	R^1	R^2	$Pd(OAc)_2$ (equiv.)	$Cu(OAc)_2$ (equiv.)	Reaction conditions	**1**-**3**, Yield (%)
a	H	H	1.0	–	117°C, 4 h, Ar	**1**, 68
a	H	H	0.1	2.5	95°C, 48 h, air	**1**, 73
b	OCH_3	H	1.0	–	117°C, 4.5 h, Ar	**2**, 71
b	OCH_3	H	0.1	2.5	117°C, 12 h, air	**2**, 44
c	OCH_3	OCH_3	1.0	–	117°C, 4 h, Ar	**3**, 73
c	OCH_3	OCH_3	0.1	2.5	117°C, 10.5 h, air	**3**, 52
c	OCH_3	OCH_3	0.2	2.5	117°C, 6 h, air	**3**, 69

For the stoichiometric cyclization the yields of the 3-methylcarbazole-1,4-quinone alkaloids (**1**-**3**) were in the range of 68-73%. The bond formation of the cyclization to **2** and **3** is regioselective for steric reasons (coupling *para* to the MeO group). The palladium(II)-catalyzed cyclization afforded the natural products in 44-73% yield. An optimization of the reaction conditions of the catalytic cyclization was performed only for murrayaquinone A (**1**) and koeniginequinone B (**3**). The present results emphasize that the palladium(II)-catalyzed cyclization with reoxidation of Pd(0) by Cu(II) is highly useful for the total synthesis of carbazole-1,4-quinone alkaloids. Many different synthetic approaches to murrayaquinone A (**1**) have been reported previously.[6,9] However, access to koeniginequinone A (**2**) and koeniginequinone B (**3**) was limited and involved, for example, a multi-step sequence by Fischer-Borsche synthesis.[7,21]
In conclusion, we have developed an efficient two-step route to murrayaquinone A (**1**) (51% overall yield based on **4a**), koeniginequinone A (**2**) (46% overall yield based on **4b**), and koeniginequinone B (**3**) (47% overall yield based on **4c**). The spectral data for all three compounds were in good agreement with those reported for the corresponding natural products.[5,7]



7 **8**

Scheme 4

Table 3. Results of the oxidative cyclization of the 6-arylamino-2-methyl-1,4-benzoquinones (**7**)

7	R^1	R^2	**8**, Yield (%)
a	H	H	69
b	OCH_3	H	84
c	OCH_3	OCH_3	65

Finally, the oxidative cyclization of the 6-arylamino-2-methyl-1,4-benzoquinones (**7**) using stoichiometric amounts of palladium(II) acetate under standard reaction conditions without further optimization provided the following 2-methylcarbazole-1,4-quinones (**8**): isomurrayaquinone A (**8a**),[18b] isokoeniginequinone A (**8b**),[18b] and isokoeniginequinone B (**8c**) (Scheme 4, Table 3).

ACKNOWLEDGEMENTS

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