Synthesis of Pyrido[3,2-*b*]carbazolequinones Involving N-Arylation of 5,8-Dimethoxy-6-nitroquinolines by Aryl Grignard Reagents and a New One-Pot, Palladium-Promoted Oxidative Coupling–Oxidative Demethylation Sequence

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Abstract: The reaction between a 5,8-dimethyxy-6-nitrocarbostyril derivative and arylmagnesium bromides gave 6-arylaminocarbostyrils as the major products. Their subsequent treatment with palladium acetate in refluxing acetic acid gave linear pyrido[3,2-*b*]carbazolequinones in one step, involving the unprecedented oxidative demethylation of 1,4-dimethoxybenzene systems to the corresponding quinones by palladium acetate. A palladium-calalyzed oxidative functionalization of an unactivated C–H bond was also observed.

Key words: N-arylation, organomagnesium reagents, palladium catalysts, oxidative demethylation, oxidative C–H activation

Compounds containing 9,10-anthraquinone substructures are important antitumor agents, the anthracyclines and mitoxantrone being representative examples (Figure 1). Their planar structures allow these compounds to act as DNA intercalating agents,[1] causing topoisomerase II inhibition,[2] and one-electron reduction of their quinone unit leads to the generation of DNA-damaging oxygen radicals.[3] Aza analogues of these compounds[4] are potentially very interesting because the presence of the nitrogen atom should increase their affinity for DNA due to the possibility of hydrogen bonding or ionic interactions, while the electron-withdrawing character of the heterocyclic rings should facilitate the formation of anion radicals. Indeed, pixantrone has shown an antitumor activity similar to that of its deaza analogue mitoxantrone, but with less toxicity, and is undergoing phase III trials for the treatment of non-Hodgkin's lymphoma.[5]

Because of the well-known DNA-intercalating properties of carbazole derivatives, exemplified by the antitumor alkaloid ellipticine,[6] carbazolequinones are particularly interesting. For instance, calothrixin B, which has been shown to induce the intracellular formation of oxygen reactive species,[7] displays a very high (nanomolar) in vitro cytotoxicity against HeLa cancer cells and it is also very interesting as a potential antimalarial agent because it inhibits the growth of a chloroquine-resistant strain of *Plasmodium falciparum*.[8] In this context, and stimulated by the excellent antitumor activity found for 2,5,8-quinolinetriones fused to a variety of rings, most notably benzene and pyridine,[9] we undertook the preparation of hybrid compounds **1** containing both substructures.

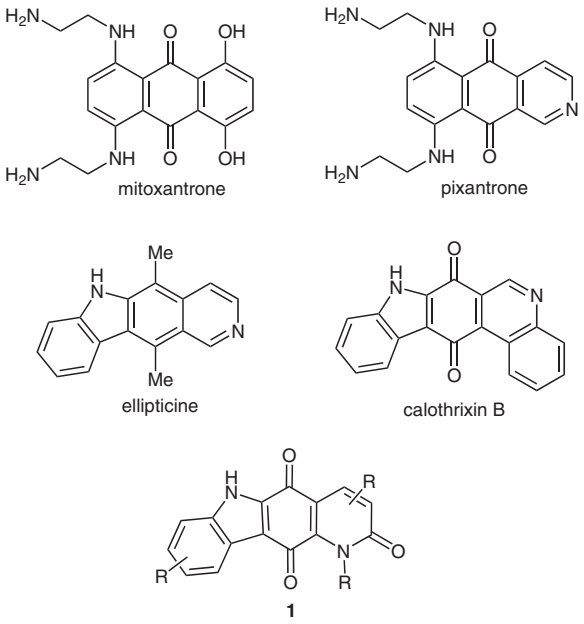

Figure 1

Our synthetic plan involved disconnection of the target structure **1** at the C–N and C–C bonds shown in Scheme 1, followed by oxidative demethylation. The N-arylation step would normally be carried out by treatment of a 6-aminocarbostyril derivative with an electrophilic arylation reagent, but we reasoned that use of the corresponding nitro compound, the most likely amino precursor, would save a step in the sequence. This led to proposing nitrocarbostyril derivatives **2** as the starting materials. The presence in these compounds of a *ortho*-methoxy group, which is important for the subsequent oxidative demethylation step, poses an interesting problem because this substituent facilitates a competing conjugate addition to the aromatic carbon β to the nitro followed by elimination of the methoxy leaving group.

In fact, this is the only pathway described in the literature for the reaction of 1-methoxy-2-nitronaphthalenes with aryl Grignard reagents, leading to 1-aryl-2-nitronaphthalenes as the sole products.[10] Although this precedent went against the viability of our planned strategy, we reasoned that it should be possible to hamper the undesired reaction

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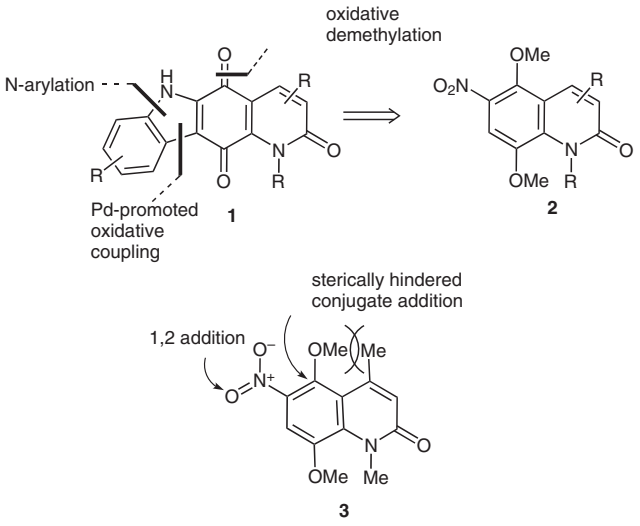
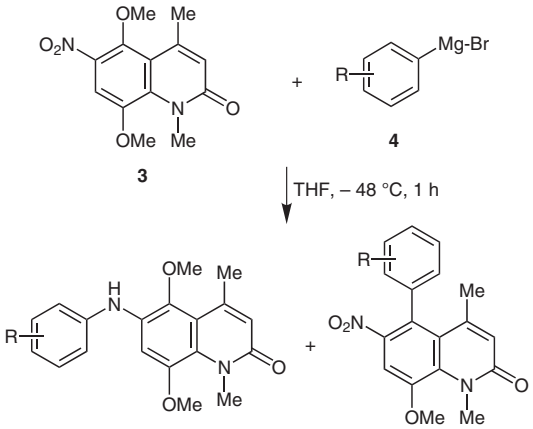


Scheme 1

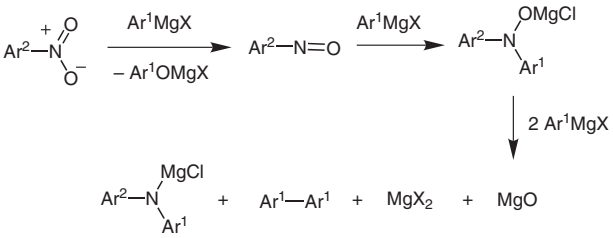
by introducing steric hindrance at the C-5 position. Therefore, we decided to employ compound **3**, bearing a methyl substituent *peri* to the methoxy group, as the substrate; this starting material was easily prepared by nitration and phase-transfer-catalyzed methylation of the known[11] 4-methyl-5,8-dimethoxycarbostyril. As expected from our hypothesis summarized above, when compound **3** was treated with 4.5 equivalents of several substituted phenylmagnesium bromides **4** at –20 °C the diarylamines **5** were isolated as the major reaction products, together with varying amounts of biaryls **6**.[12] In agreement with the expected steric effects, the highest chemoselectivity corresponded to the more hindered *o*-tolylmagnesium bromide, which gave exclusively the corresponding diarylamine **5b**, while the reactions of other aryl Grignards were less selective (Scheme 2).



	R	**5** (%)	**6** (%)
a	H	44	18
b	2-Me	63	0
c	4-Me	41	13
d	4-F	42	29

Scheme 2

The isolation of diarylamines (compounds **5**) as the major or sole products of the reaction between nitroarene **3** and aryl-Grignard compounds **4** is of interest because of the synthetic relevance of diarylamines.[13] Our experiments provide an example of the use of aryl Grignard reagents for the arylation of amines by 1,2-nucleophilic attack onto a nitro group. Although this type of arylation has been recently described, using 2.5 equivalents of Grignard reagent, the initial reaction leads to an unstable hydroxylamine derivative that requires an additional in situ reduction step.[14] We propose that the reason for the direct isolation of diarylamines under our conditions is the use of a larger excess of the starting arylmagnesium compound, which would transform the intermediate hydroxylamine species into the observed diarylamine according to the mechanism shown in Scheme 3.[15] The biaryls arising as side products in this mechanism were detected in all cases.

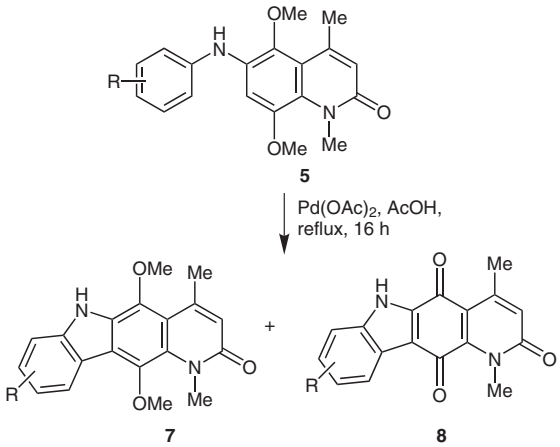


Scheme 3

We next examined the palladium-catalyzed oxidative cyclization[16] of compounds **5**, and found that, gratifyingly, their treatment with palladium acetate in refluxing acetic acid afforded the desired quinones **8** as the major products, the expected fused dimethoxycarbazoles **7** being isolated normally in low yields or not at all (Scheme 4).[17] Isolated compounds **7** could be transformed into **8** using the traditional ceric ammonium nitrate (CAN) promoted oxidative demethylation,[18] albeit in modest yield. For instance, exposure of **7d** to CAN in acetonitrile–water for one hour at 0 °C gave 38% of compound **8d**.

The *o*-tolyl derivative **5b** behaved somewhat differently, and gave a mixture of the expected methylated carbazolequinone **8c** and the (*o*-acetoxyanilino)quinolinequinone **9**, which was the major product. This compound was efficiently cyclized to the corresponding tetracyclic carbazolequinone **8e** by treatment with palladium acetate in acetic acid for an additional period of 16 hours (Scheme 5). The formation of **9** is of interest because it constitutes an example of the functionalization of an unactivated C–H bond[19] through an oxidative palladium-catalyzed reaction.[20,21]

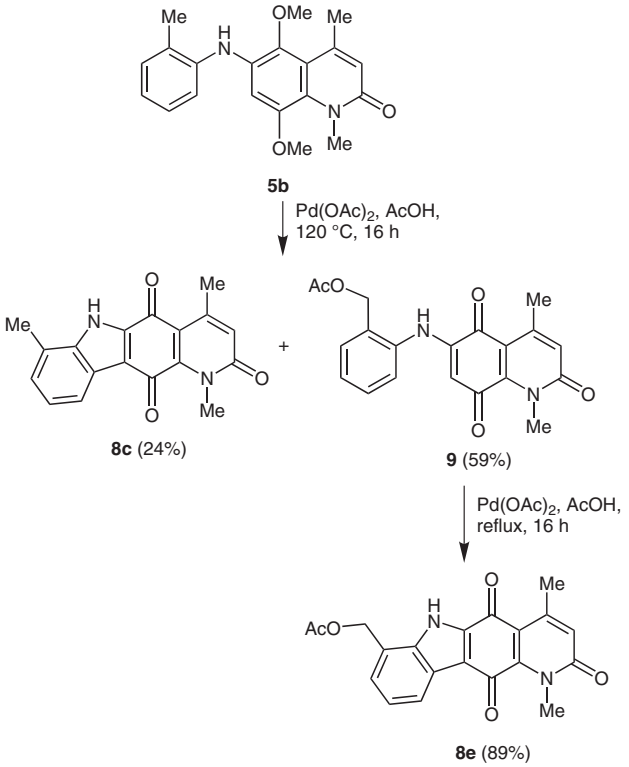
The observed in situ oxidative demethylations are unprecedented and cannot be explained by a mechanism similar to the one normally accepted for oxidative demethylation by cerium ammonium nitrate,[22] involving single-electron transfer to the organic compound coupled with a reduction



	R	7 (%)	8 (%)
a	H	25	59
c	9-Me	0	45*
d	9-F	32	47

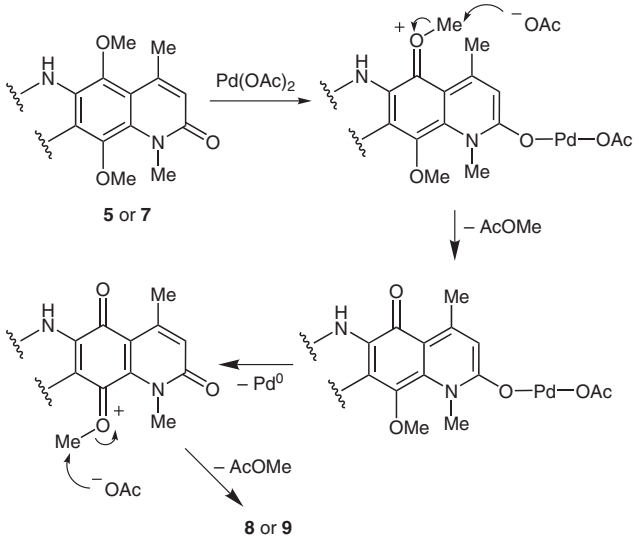
* 91% based on recovered starting material

Scheme 4



Scheme 5

from Ce^{IV} to Ce^{III}. On the other hand, reflux of compound **5c** in acetic acid for 17 hours led to unchanged starting material, and therefore an initial acid-catalyzed demethylation to a hydroquinone, followed by oxidation, can be also discarded. We propose the rationalization outlined in Scheme 6, which is based on the observation that simple diarylamines, lacking the carbostyril moiety, do not undergo the oxidative demethylation. We propose that the reaction starts by palladation of the carbonyl oxygen,[23] favored by conjugation with one of the methoxy substituents. The liberated acetate anion would then be responsible for the first demethylation. Subsequent elimination of acetate and Pd(0) would set the stage for the demethylation of the second methoxy group through a similar mechanism.



Scheme 6

In conclusion, we have developed a two-step synthesis of pyrido[3,2-*b*]carbazolequinone derivatives from readily available 5,8-dimethoxy-6-nitrocarbostyrils. Our route highlights the use of aryl Grignard compounds as N-arylation reagents and employs a protocol that avoids the need for a final reduction step, as described in the literature. Our results also demonstrate the possibility of tuning the outcome of the reaction between aryl Grignard reagents and 5,8-dimethoxy-6-nitrocarbostyril by steric effects. In the course of this work, we have also discovered an unprecedented one-pot palladium-promoted oxidative coupling–oxidative demethylation sequence yielding pyrido[3,2-*b*]carbazolequinones from 6-arylamino-5,8-dimethoxycarbostyrils in one step. A palladium-catalyzed oxidative functionalization of an unactivated C–H bond was also observed in one case where a methyl group was present *ortho* to the amino function of the diarylamine.

Acknowledgment

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(12) **Representative Procedure**
To a solution of 1,4-dimethyl-5,8-dimethoxy-6-nitro-2(1*H*)-quinolin-2-one (1 g, 3.59 mmol) was added *p*-tolylmagnesium bromide (10.8 mL of a 1 M soln in THF, 10.8 mmol). The reaction mixture was stirred at –48 °C for 1 h and poured onto a sat. aq soln of NH_4Cl (15 mL), which was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (2 × 15 mL), dried over Na_2SO_4, and evaporated. Chromatography of the residue on silica gel, eluting with a PE–EtOAc gradient, gave 534 mg (44%) of 1,4-dimethyl-5,8-dimethoxy-6-(*p*-tolylamino)-2 (1*H*)-quinolin-2-one (**5c**), as a pale brown oil, and 218 mg (18%) of 1,4-dimethyl-8-methoxy-6-nitro-5-(*p*-tolyl)-2 (1*H*)-quinolin-2-one (**6c**), as a pale brown solid.
5c: IR (KBr): 3365, 2922, 1646, 1599, 1516, 1455 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.12 (d, 2 H, *J* = 8.3 Hz, H-2′, H-5′), 7.06 (s, 1 H, H-7), 7.01 (d, 2 H, *J* = 8.3 Hz, H-3′, H-5′), 6.50 (d, 1 H, *J* = 1.0 Hz, H-3), 5.98 (br s, 1 H, NH), 3.81 (s, 3 H, NCH_3), 3.75 (s, 3 H, C5-OCH_3), 3.67 (s, 3 H, C8-CH_3), 2.60 (d, 3 H, *J* = 1.0 Hz, C4-CH_3), 2.31 (s, 3 H, C4′-CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 163.18 (CO), 145.95 (C-1′), 145.93 (C-4), 141.15 (C-8), 140.71 (C-5), 131.31 (C-6), 130.48 (C-3′, C-5′), 127.15 (C-4′), 123.82 (C-3), 118.74 (C-2′, C-6′), 118.63 (C-4a), 113.15 (C-8a), 105.93 (C-7), 61.93 (C5-OCH_3), 57.48 (C8-OCH_3), 36.39 (NCH_3), 23.68 (C4-CH_3), 21,08 (C4′-Me) ppm. Anal. Calcd for: C, 70.99; H, 6.55; N, 8.28. Found: C, 69.83; H, 6.53; N, 7.95.
6c: Mp 181–183 °C. IR (KBr): 3141, 1665, 1607, 1567, 1522 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.36 (s, 1 H, H-7), 7.18–7.14 (m, 4 H, H-2′, H-3′, H-5′, H-6′), 6.52 (d, 1 H, *J* = 0.9 Hz, H-3), 3.99 (s, 3 H, OCH_3), 3.85 (s, 3 H, NCH_3), 2.41 (s, 3 H, C4′-CH_3), 1.63 (d, 3 H, *J* = 0.9 Hz, C4-CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 162.87 (CO), 148.43 (C-8), 148.27 (C-4), 139.17 (C-6), 136.17 (C-4′), 133.17 (C-1′), 130.48 (C-3′, C-5′), 129.30 (C-2′, C-6′), 127.00 (C-8a), 125.66 (C-3), 124.10 (C-5), 123.20 (C-4a), 106.84 (C-7), 57.03 (OCH_3), 37.28 (NCH_3), 24.99 (C4-CH_3), 21,80 (C4′-CH_3) ppm. Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.83; H, 5.53; N, 7.95.

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(17) **Representative Procedure**
A solution of compound **5a** (120 mg, 0.37 mmol) and $Pd(OAc)_2$ (166 mg, 0.74 mmol) in AcOH (15 mL) was heated at 120 °C for 16 h, under an argon atmosphere. The reaction mixture was evaporated to dryness and the residue was chromatographed on silica gel, eluting with an EtOAc–PE gradient, to give 29 mg (25%) of 5,11-dimethoxy-1,4-dimethyl-1*H*-pyrido[3,2-*b*]carbazol-2 (6*H*)-one (**7a**), as an orange solid, and 64 mg (59%) of 1,4-dimethyl-1*H*-pyrido[3,2-*b*]carbazole-2,5,11 (6*H*)-trione (**8a**), as a red solid.
7a: Mp 270–272 °C. IR (KBr): 3202, 2930, 1635, 1587, 1550, 1484, 1437, 1230 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ = 8.36 (s, 1 H, NH), 7.96 (d, 1 H, *J* = 7.9 Hz, H-10), 7.51–7.57 (m, 2 H, H-7 and H-9), 7.40–7.26 (m, 1 H, H-8), 6.54 (s, 1 H, H-3), 3.99 (s, 6 H, 2 OMe), 3.85 (s, 3 H, N1-Me), 2.73 (s, 3 H, C4-Me) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 160.56 (C-2), 146.25 (C-4), 140.28 (C-11), 139.12 (C-5), 130.72 (C-6a), 128.92 (C-10a), 127.79 (C-5a), 124.02 (C-9), 122.52 (C-10), 122.29 (C-8), 120.91 (C-3), 120.63 (C-11a), 116.49 (C-7), 111.25 (C-10b), 62.35 (C5-OCH_3), 61.81 (C11-OCH_3), 36.08 (NCH_3), 23.72 (C4-CH_3) ppm. Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.70; H, 5.71; N, 8.50.
8a: Mp >300 °C. IR (KBr): 3424, 2941, 1647, 1575, 1542, 1484 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ = 12.94 (br s, 1 H, N6-H), 8.06 (d, 1 H, *J* = 7.5 Hz, H-10), 7.56 (d, 1 H, *J* = 7.5 Hz, H-7), 7.40–7.30 (m, 2 H, H-8, H-9), 6.58 (s, 1 H, H-3), 3.84 (s, 3 H, N1-CH_3), 2.56 (s, 3 H, C4-Me) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 178.01 (C-11), 177.33 (C-5), 161.37 (C-2), 149.13 (C-4), 145.89 (C-6a), 137.78 (C-10a), 136.24 (C-5a), 126,43 (C-10a), 123.99 (C-4a), 123.67 (C-9), 122.42 (C-10), 121.81 (C-8), 116.04 (C-3), 114.87 (C-10b), 113.87 (C-7), 30.68 (NCH_3), 22.59 (C4-CH_3) ppm. MS: *m/z* = 292 [M^+], 263, 169, 44. Anal. Calcd for $C_{17}H_{12}N_2O_3$: C, 69.86; H, 4.14; N, 9.58. Found: C, 69.53; H, 3.97; N, 9.24.

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