Synthesis of Oxygenated Carbazoles by Palladium-Mediated Oxidative Double C−H Activation of Diarylamines Assisted by Microwave Irradiation

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Abstract: Microwave irradiation in the presence of palladium acetate and traces of dimethylformamide allows the fast and efficient cyclodehydrogenation of diphenylamines into carbazoles. The scope of the microwave-assisted reaction is broader than that of the one using conventional conditions in that it allows the preparation of oxygenated carbazoles without apparent loss in yield. The applicability of the method to the preparation of carbazole alkaloids has been demonstrated by the development of a total synthesis of murrayafoline A, which proceeds in 50% overall yield from commercially available materials and is the shortest and most efficient route for the preparation of this alkaloid to date.

Key words: carbazoles, transition metals, microwave-assisted synthesis, cyclizations, C−H activation

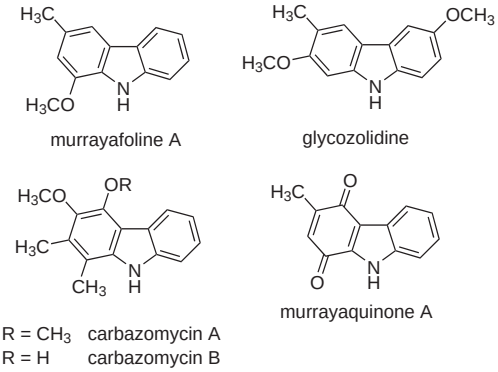

Figure 1

The carbazole alkaloids,[1] exemplified by murrayafoline A, glycozolidine, the carbazomycins and the murrayaquinones (Figure 1), are widespread in nature and have some interesting biological activities, such as the antibacterial properties of the cabazomycins.[2] A structural feature very common in these alkaloids is the presence of several hydroxy or alkoxy functions, which are sometimes oxidized to the quinone stage. Carbazoles are also increasingly important as new materials. Following the discovery of the photoconductivity of poly(*N*-vinylcarbazole), other technologically relevant properties have been described for carbazole derivatives, which have been characterized as non-linear optical[3] and photorefractive[4] chromophores. Carbazoles have been employed as a hole transporters in the design of organic electroluminescence (OEL) materials for organic light-emitting diodes (OLEDs).[5] Due to their intense native fluorescence, carbazoles are also very important as components of fluorescence sensors, including such applications as the design of fluorescent markers of cancer cells[6] or excited state proton transfer fluorescent probes for lipid bilayers.[7] Immobilized carbazoles have also interesting applications, such as their use as fluorescence carriers for the preparation of a doxycycline sensor.[8]

The practical importance of carbazole derivatives has prompted intensive research into their synthesis.[9,10] Besides the classical method based on the aromatization of tetrahydrocarbazoles obtained by Fischer synthesis, a number of strategies for carbazole syntheses based on the Diels−Alder reaction[9a] and transition-metal-mediated chemistry,[1] including methods based on the use of iron, molybdenum and palladium reagents, have been described. As part of a project aimed at the study of carbazole derivatives as fluorescent probes, we required a method for carbazole synthesis that would potentially lend itself to the future development of a fluorimetric assay for arylamines and diarylamines, which are increasingly important analytes in environmental analysis. Ideally, such synthetic method should be efficient but also as fast as possible, in order not to introduce delays in the analytical procedure. Microwave irradiation appeared to us as an ideal technique for this purpose because, when successfully implemented, it normally leads to dramatically reduced reaction times. Another advantage of microwave-assisted methodologies is the possibility of employing environmental friendly solvent-free conditions.[11] We chose as a candidate for microwave optimization the palladium-mediated cyclodehydrogenation of diarylamines to carbazoles, a reaction that involves the oxidative functionalization of the two C−H bonds adjacent to the amino group in both aromatic rings.[12] This reaction is normally carried out by refluxing together the suitable diphenylamine derivative and 1−2 equivalents of palladium acetate[13] in acetic acid. While this method is very useful for the preparation of carbazolequinones from arylaminobenzoquinones, it has an important limitation in the diarylamine case that very electron-rich carbazoles such as those bearing several alkoxy substituents conjugated with the carbazole nitrogen are difficult or impossible to obtain because of extensive decomposition of the

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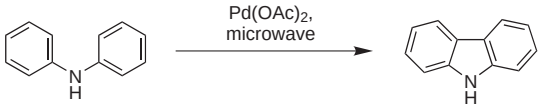
reaction products in the reaction media, presumably through oxidative pathways having a quinone imine as an intermediate. Perhaps for this reason, literature references to the preparation of polyoxygenated carbazoles by cyclodehydrogenation of diarylamines are scarce and give moderate yields.[14] We hoped that use of the milder microwave conditions could help to overcome this limitation and allow to make full use of the readily available[15] diarylamines for carbazole synthesis.

Optimization studies were performed for the transformation of diphenylamine into carbazole under microwave irradiation. As shown in Table 1, the reaction was rather inefficient when performed on mixtures of the starting material and palladium acetate because it could not be carried to completion, even using two equivalents of $Pd(OAc)_2$ and three minutes of irradiation (entries 1 and 2). A significant improvement was achieved by using a two-fold excess of palladium acetate in the presence of silica gel, as expected from a reaction that can be catalyzed by acids (entry 3), and a similar result was obtained by introducing the reaction mixture in an alumina bath during irradiation, leading to higher reaction temperatures (entry 4). One problem found under all these conditions was that the relatively long reaction times led to the occasional observation of sparks arising from Pd(0) particles generated during the course of the reaction. Based on our recent observation of the beneficial effect of the addition of small amounts of dimethylformamide in the microwave-assisted Bischler indole synthesis,[16] we studied the effect of this modification of the experimental procedure (entries 5–7), finding that it led to a 80% yield of carbazole when two equivalents of palladium acetate were employed. As in the previously studied case, we assume that this effect of dimethylformamide is associated with its role as an energy transfer agent, related to its high dipole moment and leading to an increased reaction temperature.[17] Under these modified conditions, the reaction time could be reduced to one minute and no sparking was observed.

The optimized conditions were then applied to other diphenylamines that, with the exception of those commercially available (compounds **1a** and **1b**), were prepared by reaction of the suitable aniline derivatives (containing the R^1, R^2, and R^3 substituents) with aryllead triacetates (containing the R^4 substituent) in the presence of copper diacetate, using the method developed by Barton.[18] As mentioned above, our selection of substituents was guided by the frequent presence of oxygen functions in the carbazole natural products. As shown in Table 2, besides the advantages derived from the absence of solvents and the very short reaction times required, the microwave-assisted reaction consistently gave good yields, in the 64–83% range, and was compatible with a broad range of substitution patterns, leading to carbazole derivatives containing one or two oxygen functions.[19] In those cases where the availability of literature data allowed a comparison with the conventional conditions, the yields were similar or slightly higher for the microwave-assisted reaction. Thus,

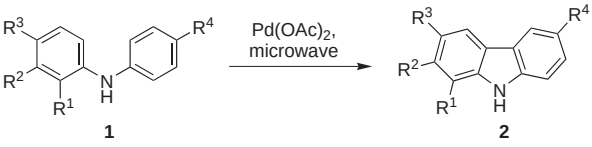
Table 1 Initial Optimization of the Cyclodehydrogenation of Diphenylamine to Carbazole



Entry	$Pd(OAc)_2$ (equiv)	Added DMF	Time (min)	Yield (%)
1	1	None	3	25
2	2	None	3	50
3[a]	2	None	2	60
4[b]	2	None	2	62
5	1	3 drops	1	53
6	1.5	3 drops	1	67
7	2	3 drops	1	80

[a] The reagents were mixed with silica gel prior to irradiation.
[b] Microwave irradiation was carried out in an alumina bath.

Table 2 Scope of the Synthesis of Oxygenated Carbazoles under Microwave Irradiation



Entry	Compound	R^1	R^2	R^3	R^4	Time (min)	Yield (%)
1	**2a**	H	H	H	H	1	80
2	**2b**	H	OCH_3	H	H	1	83
3	**2c**	H	H	OCH_3	H	1.5	76
4	**2d**	OCH_3	H	H	OCH_3	1	71
5	**2e**	H	OCH_3	H	OCH_3	1	73
6	**2f**	H	H	F	OCH_3	1	70
7	**2g**	H	OCH_2CH_3	H	OCH_3	1	81
8	**2h**	H	CH_3	H	OCH_3	1	64
9	**2i**	H	OCH_3	H	CH_3	1	70
10	**2j**	H	OCH_2CH_3	H	CH_3	1	74

compounds **2a**[20] and **2c**[21] had been previously prepared in 70% and 75% yields, respectively, after a 30 minutes reflux in acetic acid. Compounds **2b**,[21] **2e**,[22] **2h**[23] and **2i**[24] had been previously prepared using alternative methods.

One final point of interest to us was the comparison between the fluorescence of diarylamines and carbazoles. As shown in Table 3, they show clear differences in the position of both the excitation and emission maxima in several solvents and as expected the fluorescence inten-

Table 3 Comparison of the Native Fluorescences of Two Diphenylamine Derivatives and the Corresponding Carbazoles

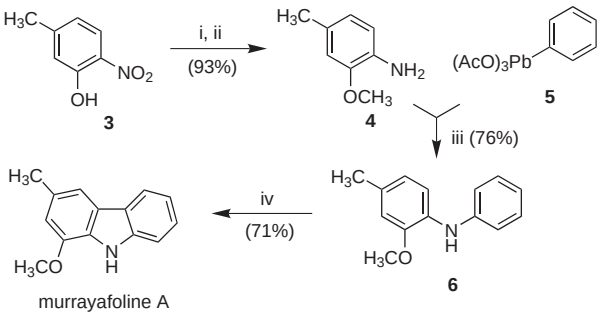
Compound	Solvent	λ_{ex}	λ_{em}	FI[a]
Diphenylamine	EtOH	295	358	1
2a	EtOH	258	340, 360	10
3-Methoxydiphenylamine	EtOH	298	358	1
3-Methoxydiphenylamine	Cyclohexane	294	357	1
3-Methoxydiphenylamine	H_2O	290−358 (broad band)		1
2b	EtOH	256, 304	344, 356	10
2b	Cyclohexane	256, 302	336, 348	10
2b	H_2O	260, 300	344, 360	10

[a] Fluorescence intensity in arbitrary units.

sity of carbazole derivatives is much higher (ten-fold) than that of the corresponding diarylamines. Hence, we expect that the microwave-catalyzed reaction can serve as a basis for the development of an analytical protocol for the quantitation of diarylamines via their transformation into carbazoles followed by chromatography with fluorimetric detection.

In order to provide a final check of the scope and flexibility of the synthetic method, we decided to apply it to the preparation of a simple carbazole natural product, and chose murrayafoline A to that effect. This compound belongs to the 1-oxygenated carbazole class of alkaloids, typically isolated from higher plants belonging to the *Murraya* genus; more specifically, murrayafoline A came from the Taiwan tree *Murraya euchrestifolia*. In spite of its simplicity, murrayafoline A has proved to be a relatively challenging synthetic target that has attracted the attention of a number of groups that have employed its preparation to illustrate a variety of carbazole synthetic protocols. These include the use of iron-mediated quinone imine cyclizations,[25] intramolecular electrophilic cyclizations of a 2-(3-formylbutyryl)indole,[9a,26] Fischer indolization,[27,28] a Horner−Emmons reaction of indole-3-carbaldehyde followed by cyclization,[29] diarylnitrenium generation from *N*-(*N*,*N*-diarylamino)phthalimides,[30] and a Diels−Alder cycloaddition of *exo*-2-oxazolidinone dienes.[31] Most of these routes are lengthy, typically involving more than five steps from commercially available materials, and suffer from low overall yields.

Our own route (Scheme 1) starts with the preparation of 4-methyl-2-methoxyaniline (**4**) by O-methylation of 5-methyl-2-nitrophenol (**3**) followed by catalytic hydrogenation. N-Arylation[32] of aniline **4** with phenyllead triacetate **5** in the presence of copper (II) acetate afforded diarylamine **6**, which had been previously prepared by an alternative method.[31] Compound **6** was cyclized to the natural product in 71% yield under our microwave-assisted conditions in one minute, while the conventional reaction proceeded in the same yield but required a ten hours of reflux in acetic acid at 140 °C.[31] The overall yield of this route was 50%, making it the most efficient synthesis of murrayafoline A to date and illustrating the way in which the efficient microwave-assisted construction of an aryl−aryl bond from readily available diarylamines leads to considerable strategic advantages in the synthesis of carbazoles.



Scheme 1 *Reagents and conditions*: i) KOH, ICH_3, $Bu_4N^+HSO_4^-$, toluene, r.t., overnight; ii) H_2, 10% Pd−C, r.t., 3 h; iii) $Cu(OAc)_2$, CH_2Cl_2, r.t., 2 h; iv) $Pd(OAc)_2$, DMF (3 drops), microwave, 600 W, 1 min.

In conclusion, microwave irradiation allows the fast cyclodehydrogenation of diphenylamines into carbazoles in the presence of palladium acetate and traces of dimethylformamide. Besides the advantages derived from the short reaction times and solvent-free conditions, the method has the advantage over the conventional one of allowing the efficient preparation of carbazoles bearing oxygenated functions, including the natural product murrayafoline A.

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(19) General procedure: The suitable diarylamine **1** (1 equiv) and palladium acetate (2 equiv) were thoroughly mixed. After addition of three drops of DMF, the mixture was irradiated in a domestic microwave oven at 600 W for 1 min or 1.5 min, as specified in Table 2. After completion of the reaction, carbazoles **2** were purified through silica gel via flash column chromatography, eluting with a PE−EtOAc (8:2) mixture.

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