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Rapid and Efficient Microwave-Assisted Copper(0)-Catalyzed Ullmann Coupling Reaction: General Access to Anilinoanthraquinone Derivatives

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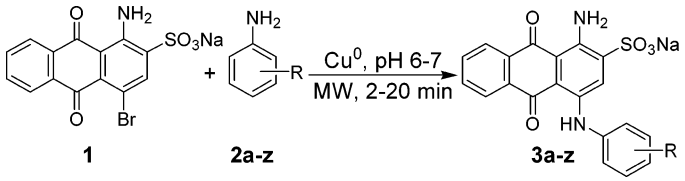
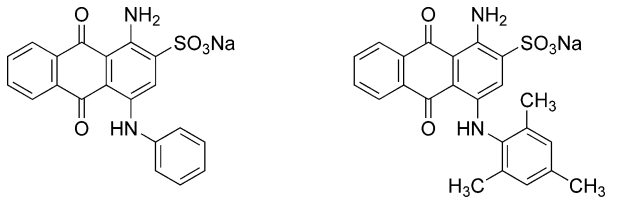
ABSTRACT



1 2a-z 3a-z

The synthesis of anilinoanthraquinones 3a–z was achieved by a new, Cu(0)-catalyzed, microwave-assisted Ullmann coupling reaction of bromaminic acid (1) with aniline derivatives 2a–z in phosphate buffer. Good to excellent isolated yields were obtained within only 2–20 min at 80–120 °C and 40–100 W. The new procedure provides the first general access to anilinoanthraquinones, furnishing a number of previously inaccessible compounds. It is superior to classical methods in all aspects, including yields, reaction time, and versatility.

Anilinoanthraquinone derivatives, such as Acid Blue 25 (**3l**) and Acid Blue 129 (**3o**) (Figure 1), have recently been identified as new lead compounds in drug discovery.[1a−e] The substitution pattern of the aniline residue was reported to play a crucial role with respect to selectivity for certain targets.[1a−e] Furthermore, anilinoanthraquinone derivatives are used for coloring natural and synthetic fibers (e.g., cotton, silk, wool, polyamide, and polyester), and there is a continuous interest in optimizing this class of compounds as documented by recent patents.[2] As a result of their significant potential as therapeutics and as coloring agents, interest has grown in the development of methods for the efficient and rapid synthesis of derivatives of anilinoanthraquinones, especially because the current methods are unsatisfactory and insufficient. The most widely employed strategy for the synthesis of anilinoanthraquinone derivatives utilizes the Ullmann coupling reaction,[3] which involves the treatment of sodium 1-amino-4-bromo-9,10-dioxo-9,10-dihydroan-



3l 3o

Figure 1. Acid Blue 25 (**3l**) and Acid Blue 129 (**3o**).

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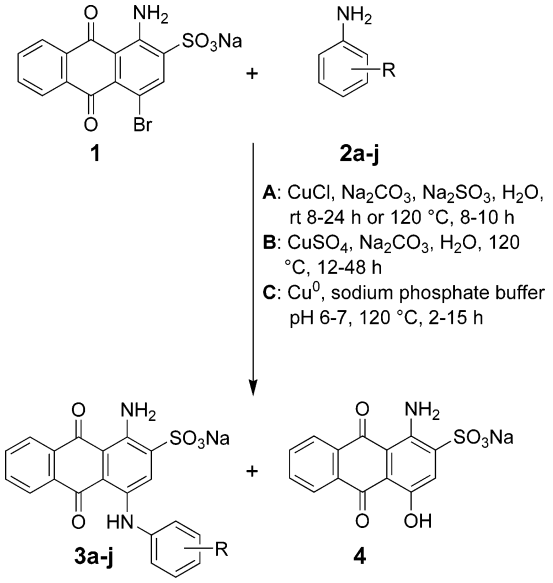
thracene 2-sulfonate (bromaminic acid sodium salt, **1**) with an arylamine in the presence of a copper catalyst (Scheme 1).[1c−f] The reaction typically requires harsh conditions, e.g.,

Scheme 1. Syntheses of Anilinoanthraquinone Derivatives



high temperatures and long reaction times, and it suffers from mostly poor yields.[1c−f]

Our group has been interested in the preparation of a series of anilinoanthraquinone derivatives derived from the dye Reactive Blue 25 (**3l**) (Figure 1) for pharmacological evaluation as antagonists of purine P2 receptors[4] and as potential ectonucleotidase inhibitors,[5] to study their structure−activity relationships.

Initially, we investigated two different classical procedures for reacting bromaminic acid sodium salt (**1**) with aromatic amines (**2a**−**j**) as outlined in Scheme 1: method A,[1c,d] reaction in the presence of CuCl, Na_2CO_3, and Na_2SO_3 in H_2O at room temperature for 8−24 h, or under reflux at 120 °C for 8−10 h; and method B,[1f] reaction in the presence of $CuSO_4$ and Na_2CO_3 in H_2O at 120 °C for 12−48 h. In many cases, no products or only poor yields could be obtained. The main undesirable product identified in all reactions was 1-amino-4-hydroxy-9,10-dioxo-9,10-dihydroanthracene 2-sulfonate (**4**, Scheme 1) formed by attack of the competing nucleophile hydroxide. A comparison of the two standard methods A and B for the preparation of a set of 10 selected compounds **3a**−**j** is shown in Table 1. Method A using copper(I) chloride as a catalyst performed in the presence of sodium carbonate and sodium sulfite did not lead to detectable conversion in most cases (monitoring by RP-TLC). Only the *p*-phenol derivative (**3j**) was obtained in a satisfactory yield of 40% (Table 1). Subsequent rise of the temperature from room temperature to 40, 60, 80, 100, up to 120 °C did not alter the yields. Results with the classical method B applying copper(II) sulfate and sodium carbonate at temperatures up to 120 °C were similarly disappointing (Table 1). A thorough search of the patent literature yielded hints that the use of Cu(0) might be advantageous.[6] We therefore performed the reactions in the presence of Cu(0) in sodium phosphate buffer, pH 6−7, at 120 °C for 2−15 h (method C).

Table 1. Comparison of Yields of Classical Methods (A and B) and Method C without or with Application of Microwaves (A^{MW}, B^{MW}, C^{MW}) for Selected Compounds

	method[a] (catalyst)					
	(CuCl)		($CuSO_4$)		(Cu^0)	
products	A[b]	A^{MW}	B	B^{MW}	C	C^{MW}
3a	0%	nd	<5%	0%	<5%	70%
3b	0%	nd	0%	0%	15%	76%
3c	0%	nd	0%	0%	<10%	70%
3d	0%	nd	0%	10%	<5%	58%
3e	0%	nd	<5%	5%	20%	70%
3f	0%	nd	0%	20%	40%	43%
3g	<10%	nd	<5%	0%	50%	64%
3h	nd	nd	nd	nd	80%	83%
3i	5%	nd	20%	60%	0%	58%
3j	40%	0%	30%	60%	0%	72%

[a] For reaction conditions A, B, and C, see Scheme 1. Reaction conditions A^{MW}, B^{MW}, and C^{MW}: same reagents as for A, B, and C, but application of microwaves, 40−100 W, 80−120 °C, 1−20 min. [b] General procedure A: rt; heating did not affect the yields significantly.

In comparison to the classical methods A and B, method C appeared to be superior. Only the phenolic products **3i** and **3j** were obtained in higher yields by methods A and B. This may be explained by the basic conditions applied in methods A and B (pH ∼ 9) but not in method C (pH 6−7). The phenolate anion formed at pH 9 increases the electron density in the ring and as a consequence increases the nucleophilicity of the amino group. Nevertheless, not only the classical methods A and B but also method C, despite its superiority, were still unsatisfactory. Recently, microwave (MW) irradiation has emerged as an efficient tool in organic synthesis, and its benefits have been well documented.[7−9] In a number of studies, it has been shown that microwave irradiation can circumvent the need for prolonged heating and it generally accelerates the rate of chemical reactions, often with increased yields. The use of MW irradiation for the formation of carbon−carbon as well as carbon−hetero-

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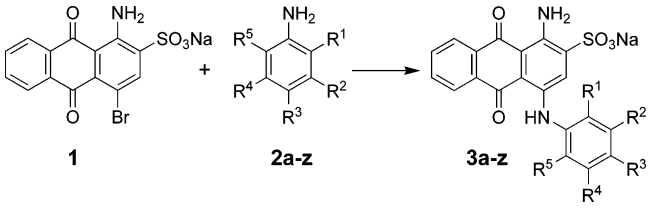
Table 2. Synthesized Anilinoanthraquinones[a]



entry	R^1	R^2	R^3	R^4	R^5	products **3** (yield [%])[b]
1	H	COOH	H	NH_2	H	**3a** (70)
2	H	COOH	H	H	H	**3b** (76)
3	H	H	COOH	H	H	**3c** (70)
4	NH_2	H	H	H	H	**3d** (58)
5	H	NH_2	H	H	H	**3e** (70)
6	COOH	H	Cl	H	H	**3f** (43)
7	COOH	H	H	Cl	H	**3g** (64)
8	COOH	H	H	H	H	**3h** (83)
9	OH	H	H	H	H	**3i** (58)
10	H	H	OH	H	H	**3j** (72)
11	H	H	NH_2	H	H	**3k** (90)
12	H	H	H	H	H	**3l** (55)
13	H	H	Cl	H	H	**3m** (87)
14	H	H	COOH	H	H	**3n** (44)
15	CH_3	H	CH_3	H	CH_3	**3o** (77)
16	OMe	H	H	H	H	**3p** (79)
17	H	OMe	H	H	H	**3q** (67)
18	H	H	OMe	H	H	**3r** (85)
19	H	H	F	H	H	**3s** (76)
20	H	Br	H	H	H	**3t** (41)
21	H	CH_3	H	CH_3	H	**3u** (32)
22	H	Cl	H	H	H	**3v** (56)
23	CH_3	NH_2	H	H	H	**3w** (34)
24	H	COOH	OH	H	H	**3x** (30)
25	SO_3H	H	H	H	H	**3y** (30)
26	H	H	SO_3H	H	H	**3z** (40)

[a] Reaction mixtures were irradiated for 2−20 min in sodium phosphate buffer, pH 6−7, in the presence of Cu^0 at 80−120 °C. [b] Isolated yields (purity of products ≥95% as determined by HPLC-UV (254 nm) ESI-MS) calculated based on educt **1**; true yields were higher because commercial **1** was only 90% pure (main contaminant: desbromo derivative, 8%).

atom bonds has been successfully demonstrated.[10,11] Thus we expected that microwave irradiation could improve the Ullmann coupling reactions. Consequently, the reaction mixtures were subjected to microwave irradiation, typically for only 2−20 min at 80−120 °C applying 40−100 W (see Table 1 and Figure 2). All other conditions (catalyst, salts, solvent) were the same as in the classical methods A and B and the improved method C. Table 1 shows the results for the 10 selected products applying methods A, B, and C compared to the corresponding microwave-assisted methods (A^{MW}, B^{MW}, and C^{MW}).

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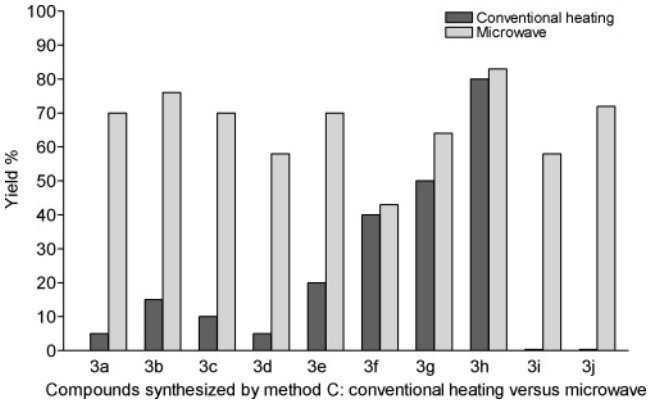
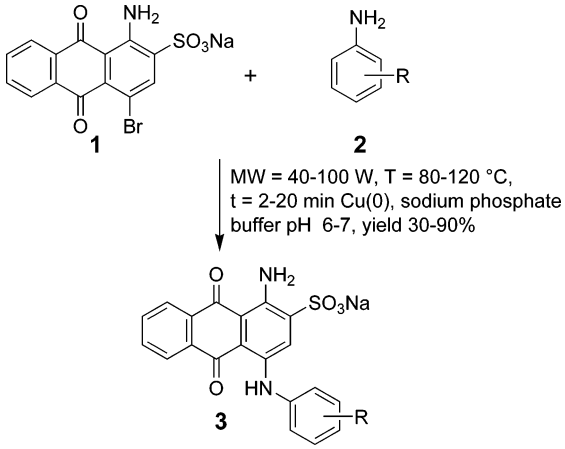


Figure 2. Comparison of yields: microwave and conventional heating using method C (Cu^0, phosphate buffer, pH 6−7).

In the case of method A, heating had not affected the yields significantly in comparison to reaction at room temperature, and therefore we applied microwaves (A^{MW}) only for one example (**3j**). In fact, microwaves even reduced the yield, probably because the degradation of bromo derivative **1** to hydroxy derivative **4** was faster under these conditions than reaction of **1** with the aniline derivative, and therefore no product of **3j** could be detected after applying method A^{MW}.

In method B, microwave irradiation (B^{MW}) in most cases moderately improved yields (Table 1). The most pronounced effect, however, was seen in combination with the superior method C. Microwave irradiation (method C^{MW}, Scheme 2

Scheme 2. Microwave-Assisted Cu(0)-Catalyzed Synthesis of Anilinoanthraquinone Derivatives in Phosphate Buffer



and Table 2) dramatically increased yields, especially of those compounds that were only poorly accessible without microwaves.

A comparison of yields obtained by methods C and C^{MW} is shown in Figure 2. For example, compounds **3a** and **3c** that could be obtained by all other methods investigated in only less than 10% yield were obtained in 70% yield by the

microwave-assisted method C^{MW}. Figure 2 also shows that the anthranilic acid derivatives **3f**−**h** were already obtained in good yields by method C without application of microwaves, which could only be slightly improved by method C^{MW}.

It should be noted that the microwave-assisted reactions were completed within 2−20 min, and longer reaction times did not increase the yields. This means there was a dramatic acceleration of the Ullmann reaction in comparison to conventional heating, which takes 2−48 h until completion.[1c−f] The superior method C^{MW} was subsequently used for the synthesis of 16 further anilinoanthraquinone derivatives (see Table 2). The desired products **3** were obtained in good to excellent yields (30−90% isolated). The main side product was the 4-hydroxyanthraquinone derivative **4** (Scheme 1) which can be recognized by its typical dark red color (RP-TLC), whereas products **3a**−**z** are blue. The commercially available starting compound **1** was only 90% pure as determined by HPLC-MS, and thus the true yields are even higher. We did not purify **1** because the contaminants (mainly the desbromo derivative) did not interfere with the investigated transformations. Reactions were typically performed using 0.2 mmol (81 mg) of starting compound **1**, but the reaction can be upscaled to multigram amounts with similarly high yields as demonstrated for several examples (compounds **3a**,**g**,**h**,**p**).

Mechanistic studies of Ullmann reactions have previously identified Cu(I) as the catalytic species under various conditions.[12] However, the formation of an organometallic intermediate from Cu(0) is also conceivable.[13]

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Future studies will be directed toward the elucidation of the mechanism of the newly developed microwave-assisted Cu(0)-catalyzed variant of the Ullmann reaction in phosphate buffer.

In conclusion, we have developed a new, fast, mild, efficient, and high-yielding procedure for the synthesis of anilinoanthraquinone derivatives, which is superior to previously published methods in all aspects, including yields, reaction time, and versatility. It is the first truly general access to this class of compounds providing access to a number of previously inaccessible derivatives. New compounds (entries 7, 9, 14, 19−21, 23, and 24) that have, to the best of our knowledge, not been described in the literature as well as several compounds (entries 1, 3, 5, 15, and 17) which have only been described in patents without a detailed description of synthetic procedures, yields, or spectral data have been prepared. The new procedure, which can easily be upscaled, may find industrial application for the preparation of dyes, and it will allow a broad evaluation of this highly promising class of potential drugs.

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Supporting Information Available: Experimental procedures and analytical data for all compounds (**3a**−**z**). This material is available free of charge via the Internet at http://pubs.acs.org.

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