Direct C–H Arylation of Quinones with Anilines

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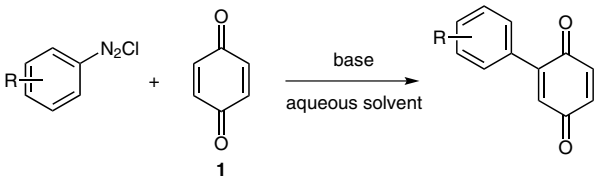
Abstract: We discovered that anilines were suitable for the direct C–H arylation of benzoquinone in the presence of *tert*-butyl nitrite. This new reaction proceeds through the in situ formation of a diazonium hydroxide species. The coupling can be carried out at room temperature under neutral, additive-free, metal-free, and aqueous conditions, allowing an environmentally friendly procedure.

Key words: quinone, aryl diazonium salt, aniline, direct C–H arylation, radical

The quinone skeleton is a privileged structure in medicinal chemistry for the discovery of pharmaceutical leads. Quinone-based compounds exhibit various important biological activities, including amongst others, antitumor,[1] antibiotic,[2] antiviral,[3] antidiabetic,[4] and antineurodegenerative[5] activities. Quinone structures are also found in many natural products including the kinamycin[6] and the mitomycin[7] families. On the other hand, due to their unique visual and electronic properties, quinone moieties are commonly used as dyes and pigments in industry. In organic chemistry, quinones are frequently used as electrophilic Michael acceptors, dienophiles for Diels–Alder reactions, and also strong oxidizing agents (chloranil, DDQ, etc.).[8] Moreover, 1,4-benzoquinone and 1,4-naphthoquinone can be used as ligands through the formation of π-complexes with transition metals.

In the course of a program devoted to the discovery of new anticancer products, we were interested in the synthesis of arylated benzoquinones. The arylation of α,β-unsaturated carbonyl compounds is commonly achieved using a palladium-catalyzed Heck reaction. Unfortunately, this reaction is inoperative with quinones due to their electronic properties and their ability to coordinate with palladium. This failure has been overcome with a prehalogenation of the quinone followed by a palladium-catalyzed Suzuki or Stille cross-coupling reaction.[9] On the other hand, the direct C–H arylation of quinones, without a prerequisite functionalization, has also been studied.[10] For instance, the reaction of free aryl radicals with quinones represents another successful alternative for such a transformation. Baran and co-workers proposed an ingenious procedure to generate aryl radicals from aryl boronic acids.[11] Their approach was likely inspired by the pioneering work of Kochi[12] and Minisci[13] on the oxidative decarboxylation of carboxylic acids by peroxydisulfate in the presence of silver(I). Some of us also reported a contribution to this reaction with the functionalization of naphthoquinones by radical decarboxylation of amino acids.[14] The direct C–H arylation of benzoquinone (**1**) has also been proposed with aryl diazonium salts (Scheme 1) in aqueous conditions and in the presence of sodium acetate. This reaction does not require any metal and can be carried out under mild conditions. Although quite convenient, this reaction requires an excess of HCl for the formation of the diazonium and a base (2–10 equiv).



Scheme 1 C–H arylation of benzoquinone (**1**) with aryl diazonium chlorides

As we were interested by the preparation of highly unstable nitro-substituted 2-arylbenzoquinones, we looked for the development of approach that could allow milder and, ideally, neutral conditions.

Our idea grew with a preliminary study by in situ ^{1}H NMR. Indeed, we observed that a mixture of the 4-methoxycarbonylaniline (**2**) and *t*-BuONO in aqueous DMSO led to the formation of the corresponding diazonium hydroxide **3** (d, 8.24 ppm and d, 8.78 ppm) along with the remaining aniline and an unidentified product (d, 7.55 ppm and d, 8.02 ppm) with a ratio of 9:52:39, after two hours of stirring (Scheme 2). Although, we were unable to unequivocally prove the structure of this latter by ^{1}H NMR due to its high reactivity, the signals at δ = 7.55 and 8.02 ppm have been tentatively assigned to the hydroxydiazene **4** or its dimer.

Based on this uncovered observation, we reasoned that the diazonium hydroxide could react with the benzoquinone (**1**), thereby, progressively displacing the equilibrium toward the desired coupling product.

We were pleased to find that our hypothesis was validated by experiments since the mixture of aniline and *t*-BuONO

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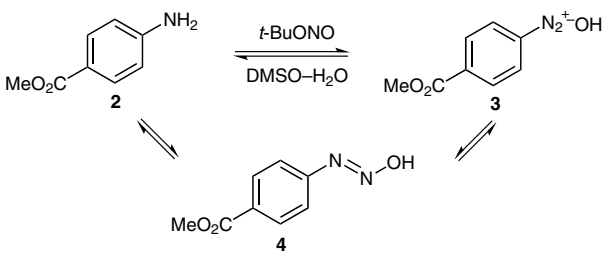
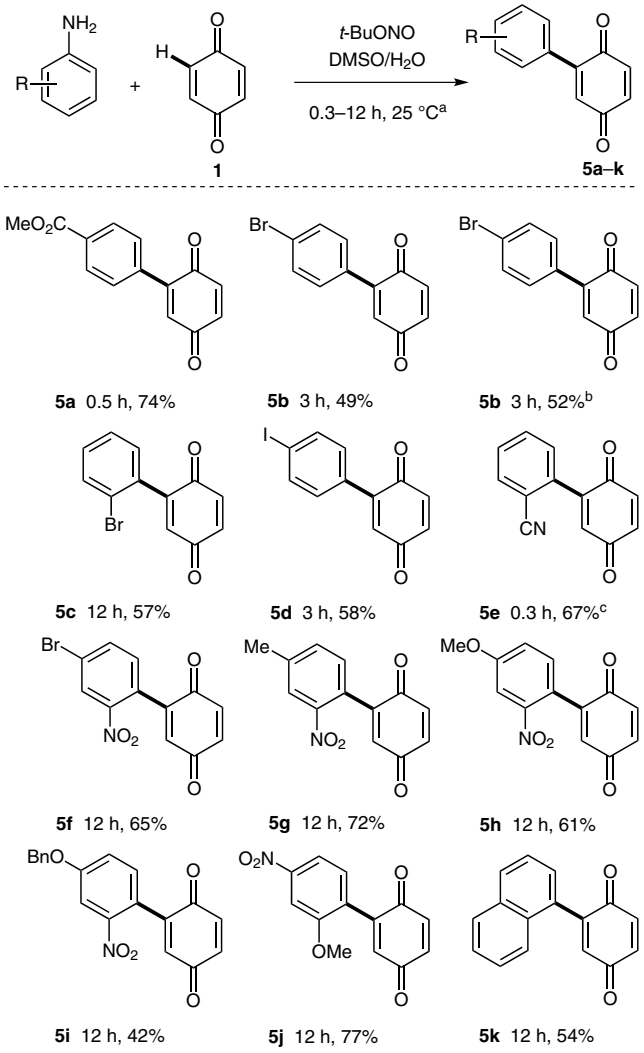


Scheme 2 Species in solution as determined by ^{1}H NMR

was effective in arylating benzoquinone (**1**, Scheme 3). The reaction is compatible with a variety of substituents including halogens (**5b–d**,**f**), ester (**5a**), cyanide (**5e**), nitro (**5f–j**), and benzyl ether (**2i**).



Scheme 3 Direct C–H arylation of benzoquinone (**1**) with anilines. [a] *Reagents and conditions*: benzoquinone (2 mmol), aniline (1 mmol), *t*-BuONO (1.5 mmol), DMSO (2 mL), H_2O (3 mL), 25 °C. [b] 4-$BrC_6H_4N_2BF_4$ was used instead of the corresponding aniline. [c] DMSO was omitted.

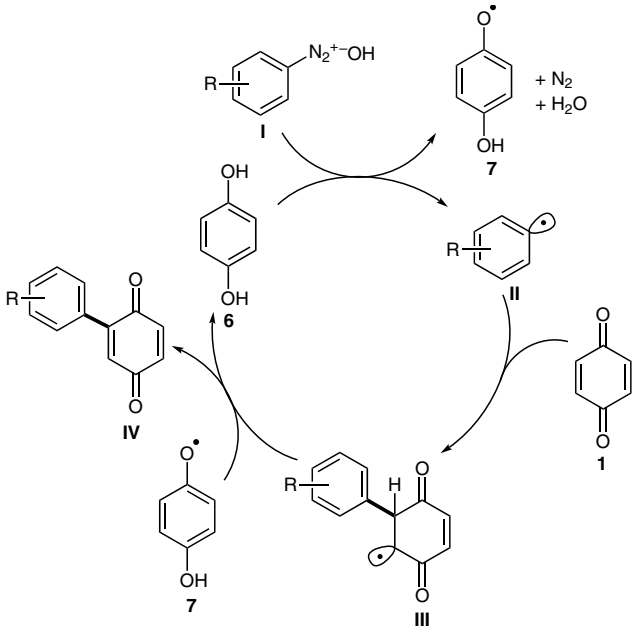
Importantly, the mild conditions used for this transformation do not affect water-sensitive functional groups such as ester and allow the preparation of sensitive nitro-substituted aryl benzoquinones. The use of pure water usually allows reaction with a similar efficiency, rendering the procedure highly valuable from a sustainable point of view (compound **5e**). However, for practical reasons, we have privileged a DMSO–H_2O mixture in which starting materials are more soluble making easier the reaction advancement analysis by TLC. By contrast, in the absence of water, the reactions failed to afford the expected quinones, highlighting the critical importance of water on the reaction outcome. Interestingly, the use of a diazonium tetrafluoroborate instead of the corresponding aniline (see compound **5b** for an example) do not significantly improve the reaction yield (52% vs. 49%). The mild conditions and short reaction times developed for this transformation tolerate reactive functions that could allow further modifications in order to prepare more elaborated compounds using standard synthetic chemistry.

This reaction is unique and represents one of the simplest entries to arylated quinones, using salt-free, metal-free, and mild conditions with inexpensive starting materials. Since the in situ generated diazonium salts are transient intermediates, this reaction represents a formally and unusual direct C–H arylation of benzoquinone (**1**) with anilines. This approach features several advantages: (1) the preparation and handling of diazonium salt can be avoided; (2) the use of corrosive HCl would be avoided; (3) the process does not form any salt and only generates *t*-BuOH, H_2O, and N_2 as benign byproducts.

The mechanism frequently invoked for the arylation of quinones involves the participation of free radical species generated by homolytic decomposition of the diazonium salt. Actually, this assumption, that has never been clearly proved, was proposed by analogy with the Meerwein arylation of olefins. However, the original Meerwein reaction uses a metal salt (Cu, Fe, or Ti) that can provide an electron.[15] In the absence of a metallic reductant, a different mechanism is necessarily operating.

It has been reported that in the absence of any metal, the heterolytic or homolytic decomposition of aryl diazonium salts is mainly governed by the pH value of the reaction mixture.[16] In general and for any kind of reaction, it is admitted that under basic conditions diazonium salts usually follow a free-radical pathway, while under acidic conditions an ionic pathway is preferred.[17] However, this empiric rule has not been validated for the specific arylation of quinones. Under neutral conditions, as developed in this work, the reactivity of diazonium salts has never been studied. In this study, we never observed the formation of phenols in the crude mixture indicating the unlikely formation of aryl cations during the reaction. As a consequence, we ruled out a cationic pathway. On the other hand, we observed that in the absence of quinone, the aniline/diazonium salt/hydroxydiazene mixture was stable at least two hours. Actually, the nitrogen evolution was observed when the benzoquinone was added to the reaction mixture. This result can be explained by a redox reaction between the diazonium salt and traces of hydroxybenzoquinone (**6**). Another explanation could in-

volve the transcient formation of the metastable benzoquinone radical cation, but the formation of this species is still the subject of debate.[18] We consistently observed that the reaction proceed in faster reaction time and better yields with aryls bearing an electron-withdrawing group. Although these results rule out any mechanism by which the aryl group could act as a nucleophile,[19] it demonstrates that a free-radical pathway is likely operating since aryl radicals are considered as electrophilic. Moreover, the higher redox potential of nitro-substituted diazonium salts favors a homolytic dediazonization pathway. Based on these observations we propose the following free-radical mechanism (Scheme 4). The homolytic dediazonization of the diazonium salt **I** would be initiated by traces of hydroxybenzoquinone (**6**). Once the free aryl radical **II** has been formed, it could react with benzoquinone (**1**) to give the intermediate **III**. This latter, upon hydrogen abstraction with the semiquinone radical (**7**), would furnish the expected arylated benzoquinone **IV**, along with the hydroxybenzoquinone (**6**) which could be involved in a further cycle.



Scheme 4 Mechanistic proposal for the direct C–H arylation of quinones

In summary, we have devised a new reaction that formally allows the C–H arylation benzoquinone (**1**) with anilines. This methodology that allow the preparation of sensitive compounds proceeds at 25 °C under neutral conditions with inexpensive reagents and without any metal and base. With the support of experimental evidences, we proposed a free-radical pathway involving a redox process initiated by trace of hydroxybenzoquinone (**6**). However, we are working on the consolidation of this proposal with the aid of computational studies. This work will be reported in due course.

Standard Procedure for the Arylation of Quinones from Anilines and *t*-BuONO

To a solution of benzoquinone (2 mmol, 2 equiv) in a 2:3 mixture of DMSO–H_2O (5 mL) were added *t*-BuONO (176 μL, 1.5 mmol, 1.5 equiv) followed immediately by a solution of aniline (1 mmol, 1 equiv) in DMSO (300 μL). The advancement of the reaction was monitored by gas evolution, and the reaction was stopped when no more nitrogen generation was observed (i.e., from 20 min to 12 h). The mixture was diluted with 20 mL of CH_2Cl_2, washed with H_2O (2 × 5 mL), brine (5 mL), dried (Na_2SO_4), and evaporated in vacuo. Purification was performed by silica gel chromatography or recrystallization to yield chromatographically and spectroscopically pure product.

2-(4-Methoxycarbonylphenyl)-1,4-benzoquinone (5a)

Quinone **5a** was synthesized following the standard procedure (reaction time: 30 min) in 74% yield after recrystallization from hexane–toluene. The spectroscopic data for these compounds were identical to those reported in the literature.[11a] R_f = 0.30 (20% EtOAc–hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (2 H, d, *J* = 8.6 Hz), 7.56 (2 H, d, *J* = 8.6 Hz), 6.95–6.83 (3 H, m), 3.95 (3 H, s). ESI-HRMS: *m/z* calcd for [M + Na^+]: 265.0477; found: 265.0473.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are experimental procedures and spectroscopic data.

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