A Direct Route to Acylhydroquinones from α-Keto Acids and α-Carboxamido Acids

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Abstract: The reaction of quinones with in situ generated acyl- or carboxamido radicals provides a direct route to the synthesis of acylhydroquinones not accessible by the photochemical reaction of quinones with aldehydes. © 1998 Elsevier Science Ltd. All rights reserved.

The synthesis of acylhydroquinones via the photochemically mediated reaction of quinones and aldehydes provides a direct and convenient synthetic method.[1] This method has the advantage of atom economy and is an environmentally benign alternative to the use of Friedel-Crafts reactions.[2] Although this method works well with aromatic and aliphatic aldehydes, it could not be extended to the synthesis of the analogous carboxamides 1 by use of substituted formamides. In the context of our interest in developing flexible routes to the pyrrolobenzodiazepine skeleton 2,[3] we recently explored the reactions of monoamides of oxalic acid as precursors to acyl radicals.
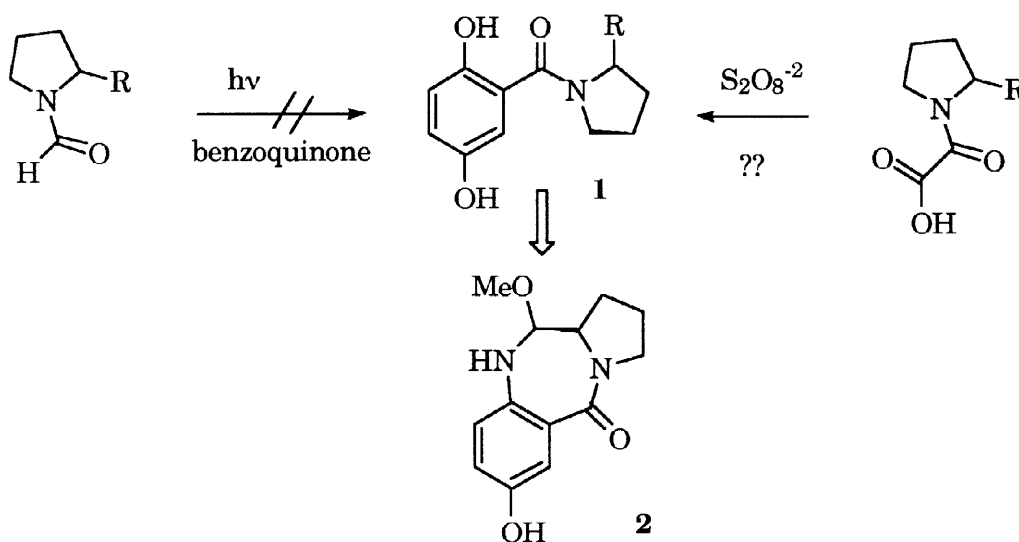
In contrast to the conventional methods for acyl radical generation such as the reaction of phenylselenoesters with organotin reagents[4] and the carbonylation of alkyl radicals,[5] the synthesis of acyl radicals from acids via the persulfate oxidation is a comparatively unexplored area. The formation of alkyl radicals from simple carboxylic acids using ammonium persulfate has good precedent.[6] Minisci had previously reported that simple monoamides of oxalic acid react with protonated heterocyclic systems in methylene chloride to afford heterocyclic carboxamides.[7] Sakamoto reported that pyruvic acid reacted with substituted pyrimidines.[8] Unfortunately, the application of these conditions to the reaction of pyruvic acid with benzoquinone led to a low yield of the desired acylhydroquinone. The persulfate reaction parameters which were varied included solvent, reaction time, equivalents of acid relative to equivalents of quinone and the amount of silver catalyst used. Minisci used an excess of the carboxylic acid component in his reactions with heterocyclic systems. In our reactions with benzoquinone, the best yields were obtained with 2-5 equivalents of quinone per equivalent of acid. Both acetonitrile and methylene chloride were tried as cosolvents for this reaction. The use of the homogeneous solvent system (acetonitrile-water) led to better yields. The results of the reactions with pyruvic acid and other α-keto acids and α-carboxamido acids are illustrated below in Table 1. These reactions were conducted on a 1-10 millimole scale.

Table 1 - The Synthesis of Acylhydroquinones by Persulfate Oxidation

3 - 10
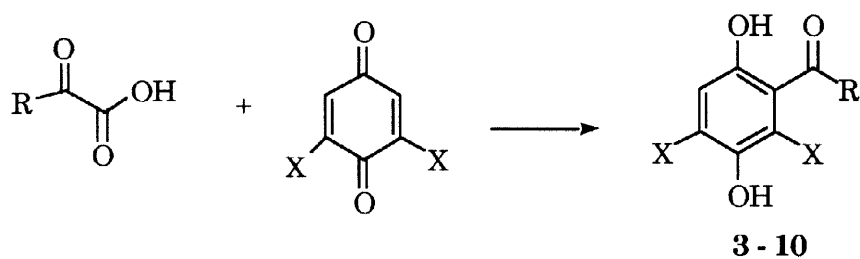
Entry	X	R	Yield	Compound
1	H	Me	92	3
2	H	Ph	73	4
3	H	Et	91	5
4	Me	Et	95[a]	6
5	H	PhCH$_2$	18	7
6	H	morpholine	53	8
7	H	iPr$_2$N	0	9
8	H	EtO	0	10

a: at 40% conversion. The product is a quinone. Reference 12 provides typical experimental conditions.

The modest yield in the reaction of phenylpyruvic acid (entry 5) is probably due to competing decarbonylation of the resulting acyl radical to a benzyl radical. The dramatic difference between entries 6 and 7 may reflect the influence of steric hindrance on a reversible reaction. A similar observation was made by Minisci.[7] The failure of the reaction involving the monoester of oxalic acid is likely due to a competing decarboxylation reaction. Interestingly, Torssell and coworkers reported the successful addition of a carboalkoxy radical to 2-benzylnaphthoquinone.[9]

With the reactions conditions now well defined, our approach to the pyrrolobenzodiazepine system began with the preparation of amide acid 11. Amide acid 11 was readily synthesized from the methyl ester of proline in nearly 95% overall yield by the reaction with BnO_2CCOCl[10] and triethylamine in methylene chloride followed by removal of the benzyl ester using catalytic hydrogenation (H_2, Pd/C in EtOAc, 2 h).[11] The reaction of acid 11 with 5 equivalents of benzoquinone using 1.2 equivalents of ammonium persulfate and a catalytic amount of silver nitrate afforded quinone carboxamide 12 in 62% isolated yield.[12] The reduction of quinone 12 using catalytic hydrogenation (Pd/C, H_2, EtOAc) followed by treatment of the resulting hydroquinone with ammonia in methanol at ambient temperature provided amide 13 in 77% yield. This compound cyclized to a bis-lactam upon treatment with silver oxide in ether. Dehydration (TFAA, Et_3N) and reduction (H_2, Pd/C) afforded compound 14.[13]
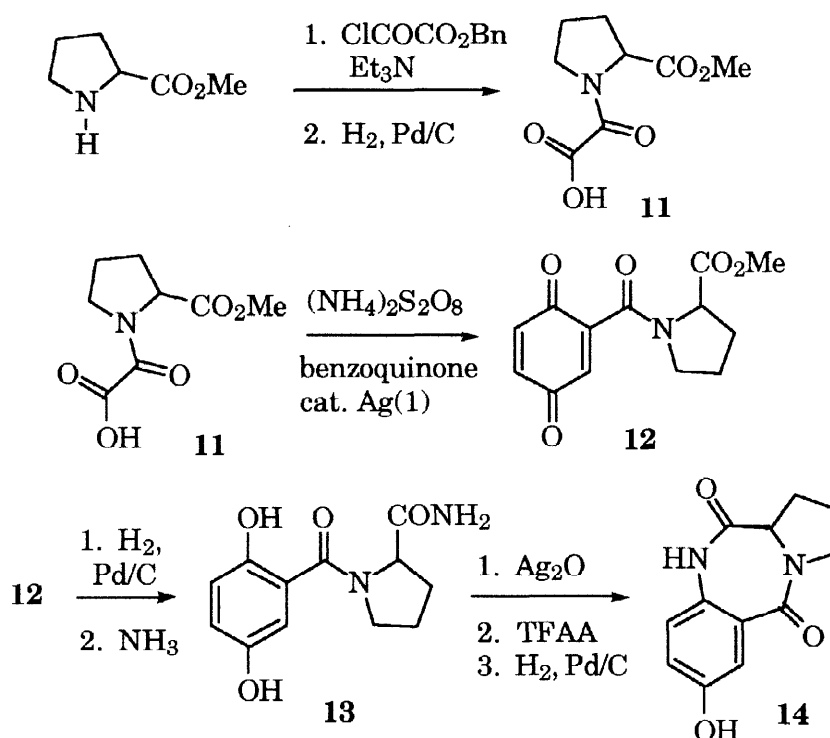
The convergent synthesis of tricyclic compound 14 is made possible by the efficient reaction of the amide acid 11 with benzoquinone. This radical reaction has the advantages of inexpensive reagents and convenient reaction conditions. The success of this key step will permit

considerable variation of substituents on the aromatic ring subunit. The selective reduction of one of the lactams to the carbinol amine has already been described.[14] This method for the synthesis of acylhydroquinones compares favorably with the photochemical method and is more environmentally benign than the corresponding Friedel-Crafts reaction.

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11. Anhydrous workup of the hydrogenation reaction was essential because of the water solubility of **3**.

12. Representative experimental: A solution of amide acid **11** (1 mmol), benzoquinone (5 mmol), ammonium persulfate (1.2 mmol) and silver nitrate (0.2 mmol) in 30 mL of 1:1 acetonitrile:water was heated at 70 °C for 2 hours. The resulting brown solution was diluted with methylene chloride. The organic layer was washed with water and dried over magnesium sulfate. After removal of the solvent in vacuo, the residue was purified by silica gel chromatography using 2:1 hexanes:ethyl acetate to afford 162 mg (62% yield) of quinone **12**.

13. Spectra for **12**: This compound is a 70:30 mixture of two rotamers. NMR (CDCl$_3$) δ 1.97-2.34 (m, 4 H), 3.30-3.35 and 3.45-3.53 (m, 1 H), 3.32-3.35 and 3.72-3.77 (m, 1 H), 3.65 and 3.77 (s, 3 H), 4.10-4.15 and 4.62-4.66 (m, 1 H), 6.67-6.84 (m, 3 H). ^{13}C NMR (CDCl$_3$) δ 22.7, 24.7, 29.3, 31.1, 46.5, 48.2, 52.6, 52.8, 58.7, 60.1, 133.1, 133.3, 136.2, 136.6, 136.7, 142.9, 143.1, 162.5, 162.6, 171.8, 172.1, 184.2, 184.4, 186.7, 186.8. HRMS: m/z calculated for M - CO$_2$Me C$_{11}$H$_{10}$NO$_3$: 204.0661; measured: 204.0657. MS (CI - NH$_3$) 264 (M+1), 281 (M+18).

    Spectra for **14**: ^{13}C NMR (CDCl$_3$) δ 25.7, 30.2, 48.2, 50.4, 114.0, 116.2, 118.4, 119.0, 121.9, 147.6, 153.8, 170.7. HRMS: m/z calculated for C$_{12}$H$_{12}$N$_2$O$_3$: 232.0848; measured: 232.0849.

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