De Novo Synthesis of α -Hydroxy Ketones via Gallic Acid-Promoted Aerobic Coupling of Terminal Alkynes with Diazonium Salts

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Abstract: An unprecedented metal-free direct preparation of unprotected α -hydroxy ketones from terminal alkynes under mild conditions with diazonium salts as the arene source and without the requirement of irradiation is described. The process is general and fully compatible with a wide variety of substitution in both reactants. Experimental and computational evidences strongly suggest the involvement of radical species in the transformation.

The occurrence of the α -hydroxy ketone framework in natural products and biologically relevant molecules,^[1] coupled to the use of this moiety as a versatile building block in organic synthesis,^[2] have led to research efforts on the preparation of α -hydroxy ketones.^[3] Usually, reported synthetic methods are tedious and present several drawbacks such as harsh conditions, low atom economy, the use of harmful reagents or transition metals, and the formation of environmentally unfriendly by-products. Aiming to surmount these shortcomings, we decided to implement a benign method for the facile preparation of functionalized α -hydroxy ketones (typical cross benzoin products).

The oxidation of organic molecules mediated by O_2 is a recent and green methodology that can be carried out at room temperature.^[4] The use of arenediazonium salts as the functionalization source may represent a non-toxic and convenient strategy, because these aryl transfer reagents release N_2 as the only waste by-product.^[5] Moreover, arenediazonium tetrafluoroborates are readily available from low-cost anilines. Although remarkable progress has been achieved in the arylation of alkynes through the use of arenediazonium salts [Scheme 1, Eq. (1), Eq. (2), and Eq. (3)],^[6] there is absence of reports on the synthesis of α -hydroxy ketones. Herein, we describe an unprecedented metal-free direct preparation of unprotected α -hydroxy ketones from terminal alkynes under mild conditions with diazonium salts as the arene source and without the requirement of irradiation [Scheme 1, Eq. (4)].

Scheme 1. Reactions of alkynes with diazonium salts.

The cytotoxicity of transition metal impurities prevents samples prepared via metal catalysis to enter biological assays. Therefore, the development of efficient metal-free strategies for the synthesis of molecules of biological interest is a growing concern these days. Inspired by previous efforts on the organomediated generation of aryl radicals from arenediazonium salts,^[7] we decided to perform a non-photochemical metal-free coupling between arenediazonium salts and alkynes solely promoted by an organic molecule. We initiated our study using phenylacetylene **1a** as the starting alkyne and phenyldiazonium salt **2a** as the arylation partner. Ascorbic acid **I**, gallic acid **II**, and benzene-1,2,3-triol **III** were selected as cheap organic promoters for the generation of radicals from arenediazonium salts by dinitrogen extrusion. After extensive solvent screening, we selected an acetone/water mixture (3:1) as the solvent of choice (Table 1, entry 2 and entries 7–10). Rather unexpectedly, the obtained product was the α -hydroxy ketone **3aa**, whose formation required the participation of both water in the solvent and oxygen from the air. The yield of benzoin **3aa** increased with the inclusion of an O_2 balloon (Table 1, entries 2 and 6). The use of excess (3 equiv) of diazonium salt was not beneficial due to the formation of diazo-derived side products (Table 1, entry 4). The inclusion of excess (3 equiv) of alkyne increased the cleanliness and the reaction efficiency to afford the desired product **3aa** in 59% yield (Table 1, entry 2). The use of a **1a**:**2a** ratio of 1:1 was less effective in this transformation (Table 1, entry 5). The optimal amount of promoters was established at 100 mol% (Table 1, entry 2). Lower loadings of **I**, **II**, or **III** resulted in diminished final yields of 2-hydroxy-1,2-diphenylethan-1-one **3aa** (Table 1, entries 11–13). Promoters **I** and **III** were found to be less effective than gallic acid (Table 1, entries 2 and 3).

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Table 1. Screening of reaction conditions for α -hydroxy ketone formation by organopromoted arylation of alkyne **1a**.^[a]

Entry	Promoter (X mol%)	t (h)	1a:2a Ratio	Yield (%) ^[b]
1	I (100)	2	3:1	45
2	II (100)	2	3:1	59
3	III (100)	2	3:1	46
4	II (100)	2	1:3	33
5	II (100)	2	1:1	41
6	II (100)	2	3:1 ^[c]	48
7	II (100)	48	3:1 ^[d]	1
8	II (100)	2	3:1 ^[e]	1
9	II (100)	24	3:1 ^[f]	12
10	II (100)	24	3:1 ^[g]	1
11	II (50)	2	3:1	26
12	II (25)	2	3:1	25
13	II (10)	2	3:1	21

[a] Unless otherwise noted, all reactions were carried out in acetone/water (3:1) in the presence of an oxygen balloon at room temperature. [b] Yield of pure, isolated product with correct analytical and spectral data. [c] Open air reaction. It was carried out without the oxygen balloon. [d] The reaction was carried out in DMF. [e] The reaction was carried out in acetone. [f] The reaction was carried out in DMF/water (3:1). [g] The reaction was carried out in acetone/MeOH (3:1).

We were curious to check whether this facile generation of 2-hydroxy-1,2-diphenylethan-1-one **3a** could be a general method for the preparation of α -hydroxy ketones. With the optimized reaction conditions in hand, we explored the scope and limitations of this transformation. The combination of alkyne **1a** with a variety of diazonium salts **2a–j** smoothly yielded α -hydroxy ketones **3aa–ai**. The results are summarized in Scheme 2. It was found that arenediazonium salts bearing either electron-withdrawing groups (CO_2Et and CF_3) or electron-donating groups such as MeO resulted in reaction success. The carboxylate derivative **3ag** was obtained in 61% isolated yield as pure product, but adducts **3af** and **3ah** were produced in diminished yields. However, the highly electron-poor nitro derivative **2j** did not afford the α -hydroxy ketone **3aj**. The steric effect was studied through the reactions of **1a** with arenediazonium salts **2b–d** bearing a Br group at *ortho*-, *meta*-, and *para*-positions. Unnoticeable differences were observed with these different substitutions in the aromatic ring. Interestingly, the C–Br bond in products **3ab–ad**, which could

serve as reactive handle for further cross-coupling reactions, survived under the above radical conditions. Interestingly, the reaction of 4-ethynylbenzenediazonium salt **2i** allows the formation of α -hydroxy ketone **3ai**, which bears an alkyne moiety. On the basis of the results in Scheme 2, both the electronic nature and the bulk of the substituent on the diazonium salt were established as not essential (except for NO_2) for the reaction to occur.

Scheme 2. Gallic acid-promoted reaction of alkyne **1a** with arenediazonium salts **2a–j**. Controlled synthesis of α -hydroxy ketones **3aa–ai**.

Next, the scope of this coupling was further evaluated by the reaction of diazonium salt **2b** with a series of alkynes having different substitution pattern (Scheme 3). The protocol was found to be general and good results were obtained in most of the cases. The reaction was found to be amenable to heterocyclic-tethered alkynes such as thiophene derivatives **1i** and **1k**. Substitution of the benzene nucleus by a naphthalene core in the alkyne was well tolerated, and the corresponding α -hydroxy ketone **1i** was achieved in 68% yield. The reaction of diyne systems **1i** and **1k** containing two alkynes tethered by an aromatic or heterocyclic ring gave in a controlled manner the mono-functionalized products **3ib** and **3kb**. This result is of potential interest because the remaining alkyne can be further elaborated. However, the dialkyne-tethered BODIPY **3l** was unreactive under the reaction conditions. Aliphatic terminal alkynes such as hex-1-yne as well as non-terminal alkynes such as 1,2-diphenylethyne were both ineffective for this transformation. Arylalkynes with a strong acceptor group at the aryl moiety (e.g., 1-ethynyl-4-nitrobenzene) did not react either under our conditions.

Scheme 3. Gallic acid-promoted reaction of alkynes **1b-I** with arenediazonium salt **2b**. Controlled synthesis of α -hydroxy ketones **3bb-kb**.

In order to gain insight regarding the mechanism of this transformation, a catalytic amount of hydroquinone was added to the reaction mixture of alkyne **1a** and diazonium salt **2a** under otherwise optimized conditions. In the event, the yield of product **3a** was considerably lower. The above result suggests that the present reaction might involve a radical process. To get some information about the origin of the oxygen atoms at the α -hydroxy ketones **3**, an isotopic labelling study with H₂¹⁸O was carried out. Unexpectedly, the reaction of **1a** with **2b** in presence of H₂¹⁸O yielded nearly unlabeled ¹⁸O-labelled product at the hydroxylic moiety ¹⁸O-**3ab**. This may be attributed to the fact that unwanted unlabeled residual water in the reaction medium reacts faster than H₂¹⁸O, avoiding high ¹⁸O atom incorporation.

Density Functional Theory calculations were carried out to gain more insight into the reaction mechanism involved in the formation of α -hydroxyketones.^[8] To this end, the reaction between phenylacetylene (**1a**) and phenyl radical (Ph[•]), initially formed upon reaction of PhN₂BF₄ and gallic acid,^[7] was explored. Our calculations indicate that the process begins with the formation of a van der Waals reaction complex (INT1) which evolves into radical INT2 in a highly exothermic process ($\Delta H_R = -46.7$ kcal/mol). This step proceeds via the transition state TS1, which is associated with the formation of the new C–C bond, with a very low activation barrier of 0.1 kcal/mol. According to the data in Figure 1, the alternative radical addition leading to the isomer INT2' (via TS1') is both kinetically and thermodynamically unfavored. Next, molecular oxygen enters into the reaction sequence and leads to the formation of the peroxy radical INT3 in a barrierless, highly exothermic process ($\Delta H_R = -34.1$ kcal/mol). Reaction of the peroxy radical INT3 with a new molecule of C-radical INT2 leads to the extremely labile peroxyde INT4 which rapidly evolves into radicals INT5 by homolytic breakage of the corresponding O–O bond in a strongly exothermic process (ΔH_R

= -46.7 kcal/mol) which constitutes the driving force of the transformation.

Figure 1. Computed reaction profile for the reaction between phenylacetylene and phenyl radical in the presence of oxygen. Relative enthalpies and bond lengths are given in kcal/mol and angstroms, respectively. All data have been computed at the PCM(acetone)-B3LYP-D3/6-311+G**//PCM(acetone)-B3LYP-D3/6-31+G** level.

According to the computed spin densities, INT5 is better described as a C-radical rather than an O-radical (due to the conjugation, see Figure 2). This species is able to react with a water molecule to produce the radical diol INT6 in a single reaction step via TS3, a saddle point associated with the simultaneous formation of the C–OH and O–H bonds. However, the computed relatively high activation barrier of 31.6 kcal/mol for this reaction makes the transformation not fully compatible with a process occurring at room temperature. Fortunately, we found that another water molecule can be involved in the transformation serving as a proton-shuttle which leads to the formation of INT6 with a much lower activation energy ($\Delta H^\ddagger = 16.7$ kcal/mol, via TS3').^[9] Finally, the transformation ends up with an intermolecular hydrogen atom transfer (HAT) mechanism involving INT6 and the gallic radical (GalO[•]), initially produced in the aryl radical generation from PhN₂BF₄ mediated by gallic acid (GalOH). This highly exothermic ($\Delta H_R = -44.3$ kcal/mol) HAT process leads therefore to the formation of the experimentally observed α -hydroxyketone **3aa** with the concomitant regeneration of gallic acid, which can enter in a new catalytic cycle.

Figure 2. Computed reaction profile for the formation of α -hydroxyketone **3aa**. Relative enthalpies and bond lengths are given in kcal/mol and angstroms, respectively. All data have been computed at the PCM(acetone)-B3LYP-D3/6-311+G**//PCM(acetone)-B3LYP-D3/6-31+G** level.

In conclusion, a metal-free direct preparation of unprotected α -hydroxy ketones from terminal alkynes under mild conditions with diazonium salts as the arene source and without the requirement of irradiation has been successfully achieved. This transformation involves the initial generation of an aryl radical which reacts with the alkyne to produce a new radical species able to react with oxygen and water to afford the observed α -hydroxyketones. With the help of DFT calculations, a proton shuttle mechanism mediated by water is suggested to be key in the formation of intermediate radical diols. Study of this reactivity in more complex molecules is planned for the future.

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