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Oxidation of Tertiary Aromatic Alcohols to Ketones in Water

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Abstract. A new rosin-based amphiphile enables the oxidation of tertiary aromatic alcohols in water under mild conditions. The oxidation process is mediated by β -scission of alkoxy radicals. Our catalyst system including the surfactant, catalysts, and water can be easily recycled within the same reaction vial.

Introduction

The oxidation of alcohols to carbonyl compounds is among the most important oxidations in organic chemistry. While numerous reagents and methods are available for converting primary alcohols to aldehydes and secondary alcohols to ketones,^[1] tertiary alcohols are generally considered to be unaffected under these conditions in textbooks on basic organic chemistry. Indeed, the oxidation of tertiary alcohols to ketones has scarcely been investigated so far,^[2] and is mainly limited to specific substrates, such as allylic alcohols, diols, and strained cyclic alcohols. In principle, ketones can be obtained from tertiary alcohols through the cleavage of adjacent C–C bonds, including β -carbon elimination (Scheme 1a)^[3] and β -scission (Scheme 1b).^[4] So far, both β -carbon elimination and β -scission strategies have been used mainly to access organometallic species^[5] radicals^[6] or alkyl for further transformations in catalysis, along with ketone byproducts.

Recently, Knowles reported a novel photocatalytic method for the oxidation of tertiary alcohols to ketones in dichloromethane (Scheme 1c).^[7] However, this β -scission reaction only applies to tertiary alcohols with an activated arene like PMP (*p*-methoxyphenyl), limiting the applicability of this elegant methodology. Herein, we present the design, synthesis, and application of rosin-based amphiphiles as a new class of "designer" surfactants, enabling the first general oxidation of tertiary aromatic alcohols to ketones via β -scission in water (Scheme 1d). These reactions proceed under aqueous reaction medium,

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which avoids some potential health, safety, and environmental issues caused by organic solvents.^[8] a) β-carbon elimination



Scheme 1. Oxidation of Tertiary Alcohols to Ketones

Results and Discussion

Initially, we started our investigation with 2phenylpropan-2-ol **1** as a model substrate, using a catalytic amount of silver nitrate (AgNO₃) together with a stoichiometric amount of potassium peroxodisulfate (K₂S₂O₈) to generate alkoxyl radicals.^[6a,9] The reaction did not take place in dry organic solvent (Table 1, entries 1 and 2). We were delighted to find that the desired oxidation reaction was feasible in organic solvent/water or pure water, albeit in low yields (Table 1, entries 3 to 5). As our continuing efforts exploring sustainable synthetic methodology in water,^[10] we further evaluated this oxidation in aqueous micellar medium. To our delight, in the presence of TPGS-750-M, a "benign-by-design" amphiphile developed by Lipshutz,^[11] acetophenone could indeed be obtained in a higher yield in water at 30 °C (Table 1, entry 6), while other surfactants afforded inferior results (Table 1, entries 7 and 8). A survey of reaction concentration and additives revealed that Bi(OTf)₃ is the preferred Lewis acid, providing the desired acetophenone oxidation product in a promising yield of 75% (Table 1, entry 11). However, the yield could not be improved further using TPGS-750-M by varying different silver salts, Lewis acids, and oxidants (see the Supporting Information). These results encouraged us to design more suitable amphiphiles for this transformation.

Table 1. Optimization of the Reaction Conditions^[a]



Entry	Additive	Solvent	Yield ^[b]
1	None	DCM ^[c]	0%
2	None	MeCN ^[c]	0%
3	None	$DCM/H_2O = 1/1^{[c]}$	19%
4	None	Acetone/ $H_2O = 1/1^{[c]}$	23%
5	None	$H_2O^{[c]}$	25%
6	None	TPGS-750-M/H ₂ O ^[c]	35%
7	None	Brij L23/H ₂ O ^[c]	27%
8	None	Tween 80/H ₂ O ^[c]	29%
9	None	$TPGS-750-M/H_2O^{[d]}$	31%
10	None	TPGS-750-M/H ₂ O ^[e]	37%
11	Bi(OTf) ₃	TPGS-750-M/H ₂ O ^[e]	75%
12	ZnCl ₂	TPGS-750-M/H ₂ O ^[e]	38%
13	FeCl ₃	TPGS-750-M/H ₂ O ^[e]	43%
14	Bi(OTf) ₃	DAPGS-750-M/H ₂ O ^[e]	90%
15	None	$DAPGS-750\text{-}M/H_2O^{[e]}$	38%

^[a] Conditions: **1** (0.3 mmol), AgNO₃ (3 mol%), $K_2S_2O_8$ (0.9 mmol), Bi(OTf)₃ (3 mol%), solvent (0.5 M), at 30 °C for 24 h. ^[b] Yields were determined by HPLC analysis with 1-nitrobenzene as an internal standard. ^[c] 0.1 M. ^[d] 0.25 M. ^[e] 0.5M. Brij L23 = polyoxyethylene (23) lauryl ether. Tween 80 = polysorbate 80.

Given the superb activity of TPGS-750-M in micellar catalysis,^[12,13] we were curious to explore if the structurally similar amphiphiles derived from dehydroabietinol would be suitable alternatives. The lipophilic dehydroabietinol portion can be easily obtained from renewable dehydroabietic acid, one of the important resin acids in rosin^[14] with an annual production of more than one million metric tons. Following a modified procedure based on Lipshutz's preparation of TPGS-750-M,^[11c] several

dehydroabietinol-polyethyleneglycol-succinate

monomethyl ethers (DAPGS) were prepared in two steps (see SI). We envisioned that DAPGS bearing a rigid inner core, dehydroabietinol without any long aliphatic chain compared to TPGS-750-M and other surfactants, would produce micelles with different shape, size, and distribution, which was comfirmed by cryogenic transmission electron microscopy (cryo-TEM, Figure 1) and dynamic light scattering (DLS) experiments (for more details, see SI). Notably, extensive aggregation of nanomicelles was observed, which might facilitate the exchange process.^[15] After the addition of AgNO₃/K₂S₂O₈/Bi(OTf)₃, particle size went up from 12 nm to 58 nm. Benevolently, DAPGS-750-M indeed gave acetophenone in excellent yield at 30 °C (Table 1, entry 14), suggesting that micellar catalysis might be playing a pivotal role in this transformation. Finally, removing Bi(OTf)₃ from the reaction led to a significantly lower yield (Table 1, entry 15), indicating there might be some co-effect Bi(OTf)₃ and DAPGS-750-M which requires further experiments to clarify.



Figure 1. Cryo-TEM images of 2 wt% DAPGS-750-M

We next explored the substrate scope of tertiary alcohols under the optimized conditions (Table 2). Model substrate 1 could be oxidized in 88% isolated yield. A high yield (90%) was obtained from the 10 mmol scale oxidation of 1, as the stirring is much more efficient for large-scale reactions. Bromoalcohols substituted benzvlic such as 2-(2-2-(3bromophenyl)propan-2-ol (2),bromophenyl)propan-2-ol (3), 2-(4and bromophenyl)propan-2-ol (4) proceeded smoothly under the standard conditions, regardless of the location of the substituent, suggesting that steric effects had little influence on the oxidation. Other halogen-substituted benzylic alcohols (5–7) gave 71%, 89%, and 48% yields respectively, thus demonstrating the tolerance of halogens and the potentiality of further functionalization. In addition, aromatic tertiary alcohols with electron-withdrawing. substituents (8-10) worked equally well as those with electron-donating groups (11 and 12). To our delight, heterocycles like 2-(thiophen-2-yl)propan-2-ol (13) and 2-(pyridin-2-yl)propan-2-ol (14) were also oxidized smoothly, leading to the desired 1-(thiophen-2-yl)ethan-1-one and 1-(pyridin-2yl)ethan-1-one respectively in moderate yield. Unsymmetrical diaryl alcohol (15) were also competent in the optimized conditions. Unfortunately, 2-(4-aminophenyl)propan-2-ol (16), bearing an free amine (NH₂), was not compatible with this reaction.

Table 2. Scope of Tertiary Alcohols^[a,b]



^[a] Conditions: alcohol (0.3 mmol), AgNO₃ (3 mol%), $K_2S_2O_8$ (0.9 mmol), Bi(OTf)₃ (3 mol%), 2 wt% DAPGS-750-M/H₂O (0.5 M) at 30 °C for 24 h. ^[b] Isolated yields. ^[c] 10 mmol scale. ^[d] 36 h.

Furthermore, we have examined tertiary arylcarbinols bearing different alkyl, alkenyl, or alkynyl groups (Table 3, 17–28). Gratifyingly, various lengths of alkyl chains showed good reactivities under the optimal conditions. Notably, neither C-phenyl bond cleavage nor C-methyl bond cleavage was observed (17-22). This highly selective C-C bond cleavage pathway is strongly suggestive of a β -scission mechanism instead of a β -carbon elimination process, as β -scission generally prefers elimination of the most stable possible alkyl radical.^[4c,d] Interestingly, 2-phenylbut-3-en-2-ol (23) and 2-phenylbut-3-yn-2-ol (24) underwent exclusive C-vinyl and C-alkynyl bond cleavages respectively. The same selectivity was observed when 3phenylpent-1-en-3-ol (25) and 3-phenylpent-1-yn-3-(26) were examined under the standard ol conditions.^[16] Remarkably, tertiary carbinols without Me substituents (27-30) successfully furnished the desired oxidation products, releasing the most stable alkyl radical.

Table 3. Further Scope of Tertiary Alcohols^[a,b]



^[a] Conditions: alcohol (0.3 mmol), AgNO₃ (3 mol%), $K_2S_2O_8$ (0.9 mmol), Bi(OTf)₃ (3 mol%), 2 wt% DAPGS-750-M/H₂O (0.5 M) at 30 °C for 24 h. ^[b] Isolated yields.

Afterward. we performed some control experiments to elucidate the reaction mechanism. Control experiments confirmed the requirement of silver potassium nitrate (AgNO₃) and both peroxodisulfate $(K_2S_2O_8)$ to generate the alkoxyl radical (Scheme 2a). Moreover, α -methylstyrene was not detected, which might rule out the possibility of a hydration step in the process. A radical pathway was further confirmed by conducting the radical inhibition experiment with radical scavenger TEMPO (Scheme 2b). Moreover, a set of Lewis acids including BiX₃, M(OTf)₃, and HOTf were examined (see the SI, Table S2) to probe the role of Bi(OTf)₃ indicating both Bi³⁺ and TfO⁻ are important for the reaction. All of them showed inferior reaction efficiency. Lastly, 2-hydroxy-1,2-diphenylpropan-1-one 31 was subjected to the standard reaction conditions, delivering acetophenone (48% yield) and benzoic acid (30% yield) along with 50% recovery of starting material (Scheme 2c). These collectively suggest that bismuth triflate/alcohol complex A may be generated first. A facile Bi–O bond homolysis^[17] subsequently would provide alkoxyl radical **B**. The alkoxyl radical **B** then undergoes β -scission to yield acetophenone and carbonyl radical C, which is further oxidized to benzoic acid.



Scheme 2. Mechanistic Investigations

To further assess the sustainability of this general methodology, we investigated in-flask recycling experiments. Once an oxidation is complete, the desired ketone product is extracted from the aqueous medium with minimal amounts of EtOAc. To the remaining aqueous mixture is then introduced arylcarbinol **4** and $K_2S_2O_8$, leading to another oxidation. As shown in Table 4, the reaction efficiency remained almost the same for three cycles, resulting in a low E factor^[18] of 11.

Table 4. E Factors and Recycling Study^[a,b]



^[a] Conditions: alcohol (0.3 mmol), AgNO₃ (3 mol%), $K_2S_2O_8$ (0.9 mmol), Bi(OTf)₃ (3 mol%), 2 wt% DAPGS-750-M/H₂O (0.5 M) at 30 °C for 24 h. ^[b] Isolated yields.

Conclusion

In summary, we have introduced a new rosin-based surfactant DAPGS-750-M, which enabled a general oxidation of tertiary aromatic alcohols to ketones in water. A variety of tertiary arylcarbinols can be oxidized to ketones in good to high yields. In addition, our surfactant would be complementary to the wellknown TPGS-750-M and others used in micellar catalysis. Notably, this oxidation methodology utilizes an aqueous reaction medium, allowing for inflask recycling of the DAPGS surfactant, catalyst and water. Further applications of our new surfactant and variations will be published in due course.

Experimental Section

General procedure for oxidation of tertiary alcohols:

A Nitrogen flashed vial was charged with AgNO₃ (1.6 mg, 3 mol%), Bi(OTf)₃ (6 mg, 3 mol%) and $K_2S_2O_8$ (245.8 mg, 3 eq), followed with 2 wt% DAPGS-750-M/H₂O (0.6 mL, 0.5 M) and alcohol (0.3 mmol). The solution was stirred at 30 °C until completed. The solution was then exacted with EtOAc, dried over anhydrous Na₂SO₄, concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (5% to 10% ethyl acetate in petroleum ether) to afford desired products.

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