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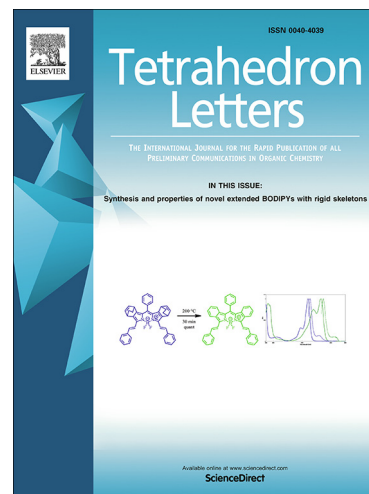
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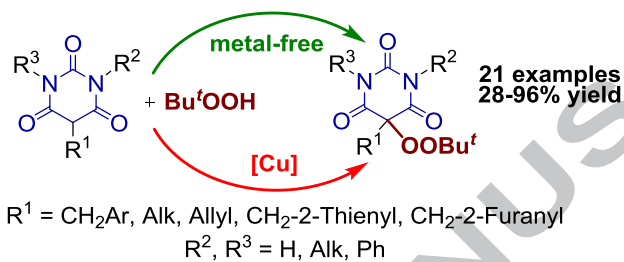
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Kharasch reaction: Cu-catalyzed and non-Kharasch metal-free peroxidation of barbituric acids

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Dedicated to Prof. Gennady I. Nikishin on the occasion of his 90th birthday.

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ABSTRACT

It was discovered that the Kharasch peroxidation of barbituric acids proceeds both with a Cu-catalyst and without a metal catalyst. Despite the presence of possible thermal-initiated side oxidation pathways, α -*tert*-butylperoxybarbiturates were selectively prepared from substituted barbituric acids and *tert*-butyl hydroperoxide.

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Kharasch peroxidation

barbituric acids

oxidative C-O coupling

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Introduction

The selective formation of chemical bonds with high atom efficiency is one of the most challenging chemical problems.¹⁻² Oxidative cross-coupling represents an elegant approach to achieve this purpose.²⁻⁴ Despite significant progress in oxidative cross-coupling over the past decades,⁵⁻⁶ selective activation and transformation of the required C-H bond remains a challenging task.⁷ The oxidative coupling with C-O bond formation⁸ is the least studied and most difficult to perform among all types of oxidative coupling.⁹⁻¹⁴

The most developed field of organic peroxide usage is as radical initiators in industrial processes for the manufacture of polymers from unsaturated monomers.¹⁵⁻¹⁶ In the past decades, the rapid development of organic peroxides in medicinal chemistry¹⁷⁻²⁰ has been observed due to their potential as drugs against parasitic diseases, such as malaria²¹⁻³³ and helminth infections.³⁴⁻³⁷ Peroxides exhibiting antitumor³⁸⁻⁴¹ and growth-regulatory activities⁴²⁻⁴⁴ were also discovered. Success in medicinal chemistry stimulates the development of new methods for the synthesis of organic peroxides, preferably from readily available starting substrates: ketones,⁴⁵⁻⁴⁸ acetals⁴⁹⁻⁵⁰ and carboxylic acid derivatives,⁵¹⁻⁵² using oxygen,⁵³⁻⁵⁵ ozone,⁵⁶ hydrogen peroxide,⁵⁷⁻⁵⁸ and hydroperoxides.⁵⁹⁻⁶¹

The Kharasch reaction, discovered more than sixty years ago, is the first example of an oxidative C-O coupling process.⁶²

In this reaction the transition metal / hydroperoxide system is used for the introduction of an alkylperoxy moiety to alkenes,

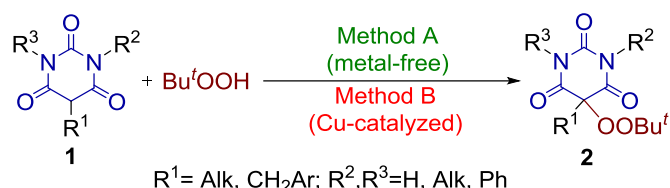
ketones and tertiary amines.⁶³⁻⁶⁴ Today it is known that peroxide synthesis can be carried out using hydroperoxides in combination with various metal salts and their complexes: copper,⁶⁵⁻⁷¹ cobalt,^{68, 72-75} manganese,⁷⁶⁻⁷⁷ ruthenium⁷⁸ and iron,⁷⁹⁻⁸³ including metalloporphyrins,⁸⁴ dinuclear nickel complexes,⁸⁵ palladium acetate⁸⁶ and ruthenium(II)-bipyridine,⁸⁷ as well as with iodine-containing compounds.^{52, 88-91} Thus, a general characteristic of the Kharasch reaction is the application of metal containing compounds. One of the main ideas of our work is the exclusion of metal containing compounds from the peroxidation process. To the best of our knowledge, for more than the half a century history of the Kharasch reaction, only one catalyst-free peroxidation with hydroperoxides has been described in the literature using the example of 3-substituted indolin-2-ones.⁹²

Substituted barbituric acids were selected as substrates for the study of radical peroxidation. The development of new methods for barbituric acid derivative synthesis is highly important due to their action on the central nervous system⁹³⁻⁹⁵ and other recently discovered bioactivities.⁹⁶ Previously, the peroxidation of α -substituted barbituric acids was carried out using a Fe(II) salt / TBHP system.⁹⁷ Herein, we report the peroxidation of α -substituted barbituric acids using either a Cu(II) catalyst or under metal-free conditions. To the best of our knowledge, the C-H peroxidation of barbituric acids under metal-catalyzed or metal-free conditions has not been described.

Results and Discussion

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We found that Bu^tOOH can be used for the peroxidation of α -substituted barbituric acids **1** with or without Cu(II) salts to give target peroxides **2** (Scheme 1).



Scheme 1. Peroxidation of α -substituted barbituric acids using a Cu(II) catalyst as well as under metal-free conditions.

We chose the model reaction of α -benzyl barbituric acid **1a** with *tert*-butyl hydroperoxide (70% in water) affording α -benzyl-*tert*-butylperoxybarbiturate **2a** for the optimization of peroxidation conditions (catalyst, solvent, temperature, amount of TBHP) (Table 1).

Table 1. Peroxidation of α -benzyl barbituric acid **1a** with *tert*-butyl hydroperoxide.^a

Entry	Molar ratio: moles TBHP per mole 1a	Catalyst	Time (h)	Yield 2a (%)
1	3	Cu(ClO ₄) ₂ ·6H ₂ O	0.5	63
2	3	Cu(OAc) ₂ ·H ₂ O	0.5	55
3	3	CuCl ₂ ·2H ₂ O	0.5	58
4	3	CuSO ₄ ·5H ₂ O	0.5	76
5	3	Cu(NO ₃) ₂ ·7H ₂ O	0.5	65
6	3	Cu(BF₄)₂·6H₂O	0.5	81
7	3	FeCl ₂ ·4H ₂ O	0.5	36
8	3	Fe(ClO ₄) ₃ ·8H ₂ O	0.5	60
9	3	Mn(OAc) ₃ ·2H ₂ O	0.5	41
10	3	Mn(OAc) ₂ ·4H ₂ O	0.5	50
11	3	Ni(OAc) ₂ ·4H ₂ O	0.5	12
12	3	Co(NO ₃) ₂ ·6H ₂ O	0.5	68
13	3	Cu(BF ₄) ₂ ·6H ₂ O	1	80
14	3	Cu(BF ₄) ₂ ·6H ₂ O	2	75
15	5	Cu(BF ₄) ₂ ·6H ₂ O	0.5	73
16	5	Cu(BF ₄) ₂ ·6H ₂ O	5	59
17 ^b	3	Cu(BF ₄) ₂ ·6H ₂ O	0.5	trace
18 ^c	3	Cu(BF ₄) ₂ ·6H ₂ O	0.5	37
19	3	-	1	10
20	3	-	2	58
21	3	-	5	59
22	5	-	2	63
23	5	-	5	91
24 ^b	5	-	5	n.d.
25 ^c	5	-	5	n.d.
26 ^d	5	-	5	68
27 ^e	5	-	5	76
28 ^f	5	-	5	30

^a General reaction conditions. The catalyst (0.1 mmol, 0.1 eq.) and a 70% aqueous Bu^tOOH solution (3.0-5.0 mmol, 3.0-5.0 eq.) were added to a solution of α -benzyl barbituric acid **1a** (1.0 mmol, 246.3 mg, 1.0 eq.) in CH₃CN (5 mL). The reaction mixture was heated at reflux for 0.5-5 h. Isolated yield. ^b 25°C. ^c 50°C. ^d EtOH (5 mL) solvent. ^e THF (5 mL) solvent. ^f DCE (5 mL) solvent.

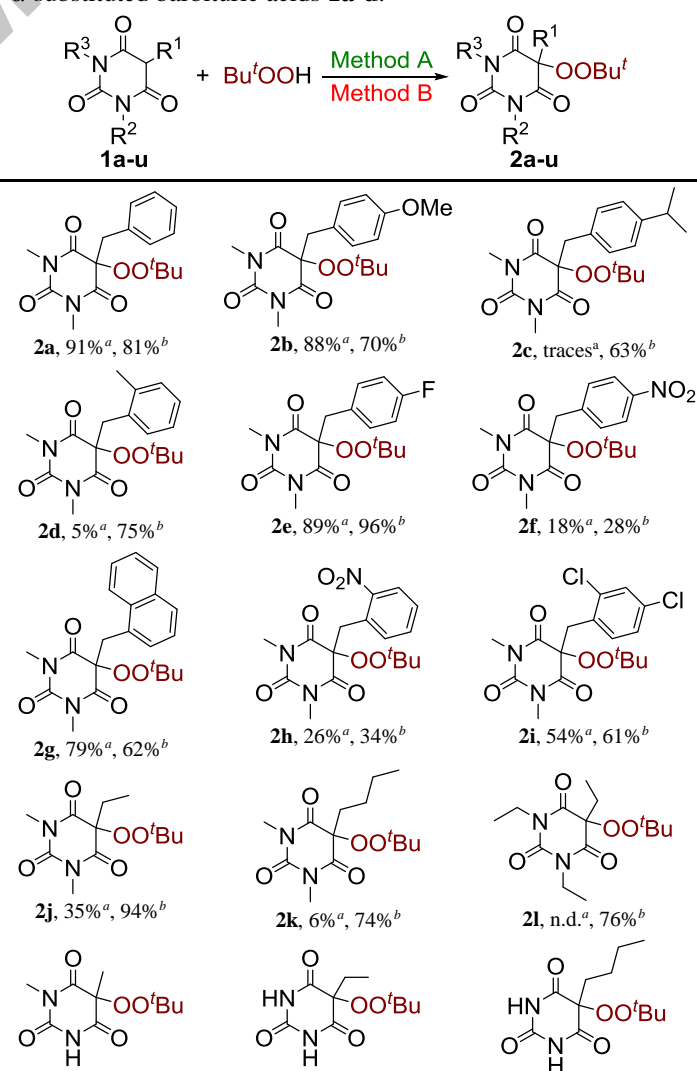
Firstly we used Cu(II), Fe(II) and Fe(III), Mn(II) and Mn(III), Ni(II), and Co(II) salts as catalysts for the peroxidation of α -benzyl barbituric acid **1a** (Table 1, entries 1-12). The best result

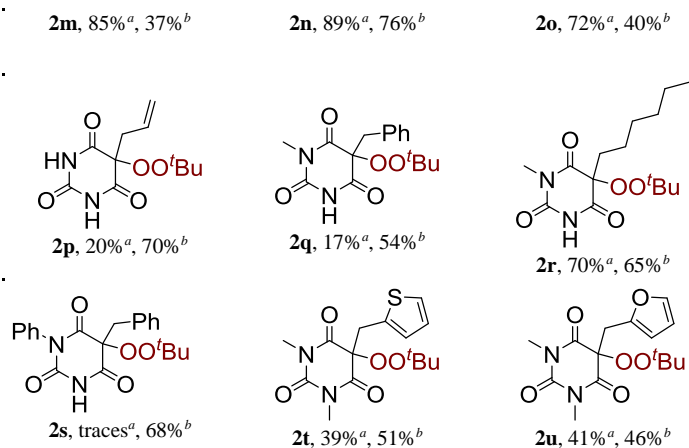
was achieved with copper(II) tetrafluoroborate hexahydrate as a catalyst (Table 1, entry 6), which gave the target α -benzyl- α -*tert*-butylperoxybarbituric acid **2a** in 81% yield. The influence of the reaction time was demonstrated in entries 6, 13, 14 (Table 1). When the reaction time was increased to 1 h, the yield of product **2a** did not significantly change (80%, entry 13). Further increasing the reaction time resulted in a reduced product yield (72%, entry 14). Increasing the amount of TBHP did not lead to an increase in the yield of **2a** (Entries 15-16). An attempt to perform the peroxidation at lower temperature instead of at reflux showed that the latter was essential for achieving high product yields (Entries 17 and 18).

Next, we examined the peroxidation of α -benzyl barbituric acid **1a** by TBHP under catalyst free conditions (Entries 19-28). Surprisingly, we observed the formation of **2a** in moderate yield (58-59%, entries 20, 21) albeit with increased reaction times. Paying attention to this result, we examined the influence of the other factors on the yield of target peroxide **2a** under metal free conditions (Entries 22-28). The yield of **2a** increased to 91% when 5 eq. of TBHP was used and the reaction was carried out for 5 hours (Entry 23). DCE, THF or EtOH proved to be poor solvents for this reaction (Entries 26-28).

The optimal reactions conditions (Method A – Table 1, entry 23 and Method B – Table 1, entry 6), were utilized for the synthesis of peroxides **2a-u** with various types of substituents (Table 2).

Table 2. Structures (and yields) of peroxides **2a-u** derived from α -substituted barbituric acids **1a-u**.^a

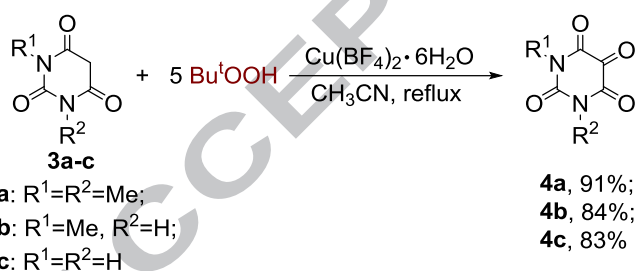




General reaction conditions. ^a Method A: A 70% aqueous Bu^tOOH solution (5.0 mmol, 5.0 eq.) was added to a solution of α -substituted barbituric acids **1a-u** (1.0 mmol, 156.1-315.2 mg, 1.0 eq.) in CH₃CN (5 mL). The reaction mixture was heated at reflux for 5 h. ^b Method B: A 70% aqueous Bu^tOOH solution (3.0 mmol, 3.0 eq.) was added to a solution of α -substituted barbituric acids **1a-u** (1.0 mmol, 156.1-315.2 mg, 1.0 eq.) and Cu(BF₄)₂·6H₂O (0.1 mmol, 34 mg, 0.1 eq.) in CH₃CN (5 mL). The reaction mixture was heated at reflux for 0.5 h.

The preparation of α -*tert*-butylperoxybarbiturates **2a-u** with electron withdrawing (**2e**, **2f**, **2h**, **2i**), electron donating (**2b-d**) benzylic (**2a**, **2q**, **2s**), naphthyl (**2g**), alkyl (**2j-o**, **2r**), allyl (**2p**), thiophene (**2t**) and furan (**2u**) groups generally proceeded with good or high yield using both methods (Table 2). The Cu-catalyzed method (Method B) appears to be more reliable because peroxides **2a-u** were prepared in 28-96% yield and unsuitable substrates **1** were not found. The metal-free method (Method A) usually showed yields of comparable to method B. However, poor results were obtained for products **2c**, **2d**, **2k**, **2l** and **2s**.

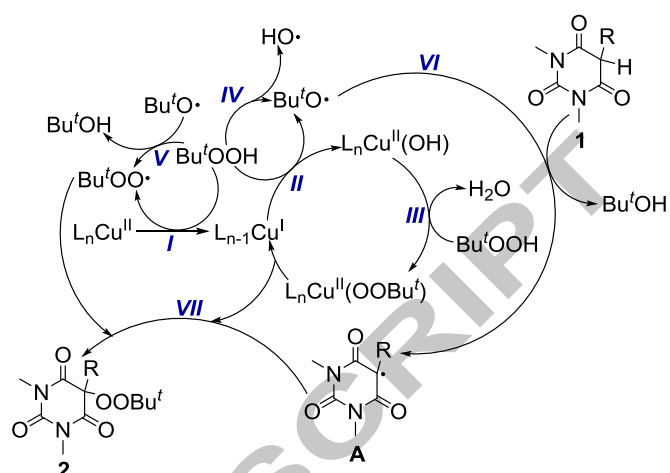
In the case of the peroxidation of α -unsubstituted barbituric acids **3a-c**, oxidation products **4a-c** were obtained in 83-91% yield (Scheme 2). It should be noted that the reactions of unsubstituted barbituric acids **3a-c** proceed only in the presence of copper(II) tetrafluoroborate hexahydrate as the catalyst.



Scheme 2. Oxidation of α -unsubstituted barbituric acids **3a-d** using *tert*-butyl hydroperoxide.

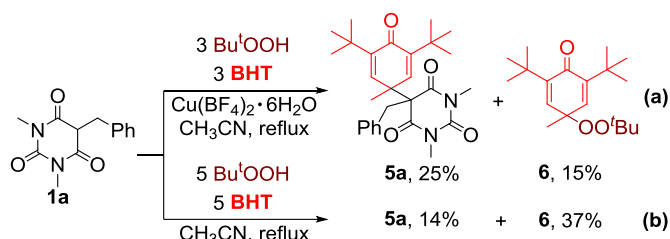
Taking into account the published data,⁹⁸⁻¹⁰² it can be suggested that the peroxidation of α -substituted barbituric acids **1a-u** occurs according to Scheme 3. Initially, Cu(II) oxidizes Bu^tOOH to the Bu^tOO radical to form monovalent copper (step I).^{65, 84, 103} Next, monovalent copper is oxidized by *tert*-butyl hydroperoxide to give Cu(II) and the Bu^tO radical (step II). This Cu(II) species reacts with TBHP to form a copper TBHP complex¹⁰⁴ (step III). The decomposition of TBHP at an elevated temperature also leads to the formation of Bu^tO radicals (step IV), which allows the reaction to be carried out without transition metal salt catalysis.¹⁰⁵ The Bu^tO radical abstracts a hydrogen atom from the *tert*-butyl hydroperoxide molecule to form the Bu^tOO radical (step V) or from α -substituted barbituric

acid **1** to form radical intermediate **A** (step VI). Finally, radical **A** couples with the Bu^tOO radical or its metal complex Cu(II)(OO^tBu) to afford the peroxidation product **2** (step VII).⁹⁷



Scheme 3. Proposed reaction mechanism of peroxidation of barbituric acids both with Cu-catalyst and without metal catalysis.

We then tried to confirm the formation of intermediate **A** and the *t*-BuOO radical. For this purpose, the peroxidation of barbituric acid **1a** was carried out in the presence of the radical scavenger BHT (2,6-di-*tert*-butyl-4-methylphenol) under both Cu-catalyzed conditions and metal-free conditions (Scheme 4). In both cases, the formation of product **2a** was not observed. Product **5a** (the coupling product of BHT with intermediate **A**) and peroxide **6** (the coupling product of BHT with the *t*-BuOO radical) were isolated, which confirmed the involvement of radical pathways.



Scheme 4. Control experiments for the peroxidation of barbituric acid **1a** in the presence of a radical scavenger.

Conclusion

It was discovered that the Kharasch-type peroxidation of α -substituted barbituric acids with formation of α -*tert*-butylperoxy- α -substituted barbiturates can be performed under both Cu-catalyzed conditions and metal-free conditions. A broad scope of α -*tert*-butylperoxy- α -substituted barbiturates was synthesized with 28-96% yield. Moreover, using experimental data and previous reports plausible radical reaction mechanism that involves both the metal-catalyzed pathway and the thermal initiation pathway was proposed. A remarkable finding of the work is in that the Kharasch reaction which selectivity is traditionally provided by metal or iodine-containing compounds can be selectively carried out under thermal initiation. The developed peroxidation opens the door for the discovery of additional thermal metal-free selective reactions with hydroperoxides.

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Supplementary data

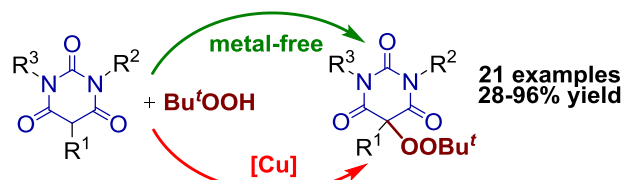
Supplementary data (the general experimental methods and the ^1H NMR, ^{13}C NMR and HRMS data) associated with this article can be found, in the online version, at <http://.....>

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R¹ = CH₂Ar, Alk, Allyl, CH₂-2-Thienyl, CH₂-2-Fyranyl
R², R³ = H, Alk, Ph

Highlights

Kharasch reaction in non-Kharasch conditions

Metal-free peroxidation

Barbituric acids

ACCEPTED MANUSCRIPT