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Synthesis of Asymmetric Peroxides: Transition Metal (Cu, Fe, Mn, Co) Catalyzed Peroxidation of β-Dicarbonyl Compounds with *tert*-Butyl Hydroperoxide

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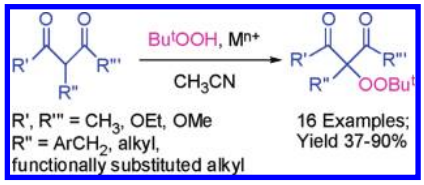

The transition metal (Cu, Fe, Mn, Co) catalyzed peroxidation of β-dicarbonyl compounds at the α position by *tert*-butyl hydroperoxide was discovered. A selective, experimentally convenient, and gram-scale method was developed for the synthesis of α-peroxidated derivatives of β-diketones, β-keto esters, and diethyl malonate. Virtually stoichiometric (2−3/1) molar ratios of *tert*-butyl hydroperoxide and a dicarbonyl compound were used in the reactions with β-diketones and β-keto esters. The target compounds were synthesized in the highest yields from β-keto esters (45−90%) and in somewhat lower yields from β-diketones (46−75%) and malonates (37−67%).

Introduction

In the past decades, organic peroxides have received considerable attention from chemists and drug design experts because of their potential as drugs for the treatment of parasitic diseases, such as malaria[1,2] and helminth infections.[3] Considerable progress has been made in the design of effective peroxide antimalarial drugs. Thus, the natural peroxide artemisinin and its semisynthetic derivatives are widely used in medicine. Some synthetic peroxides exhibit activity equal to or higher than that of artemisinin.[4] Peroxides having antitumor[5] or growth-regulatory activity[6] were also documented.

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As a result of their availability and high efficiency, organic peroxides play a leading part as radical polymerization initiators in the industrial synthesis of such polymeric materials as polyacrylates, polystyrene, styrene-containing rubbers, and high-pressure polyethylene and are also used as cross-linking agents.

The design of peroxide-based explosives is of particular interest. Triacetone triperoxide is one of the most sensitive known explosives with an explosive power similar to that of trinitrotoluene.[7] Peroxide derivatives of other lower ketones and aldehydes can also be of interest as high-energy substances.

The present study is a continuation of our research on the peroxidation of β-dicarbonyl compounds.[8] It was found for the first time that transition metals (Cu, Fe, Mn, and Co) catalyze the selective peroxidation of β-dicarbonyl compounds at the α position by *tert*-butyl hydroperoxide.

The transition metal (Cu, Mn, Co)/hydroperoxide system was used for the first time by Kharasch in the synthesis of peroxides from alkenes, ketones, and tertiary amines more than six decades ago.[9] Since that time, the research on and application of this peroxidation method have been documented in numerous publications. The formation of peroxides has been observed in various reactions of hydroperoxides catalyzed by metal salts and their complexes: copper,[10] cobalt,[11] and iron,[12] including Gif[13] and metalloporphyrin[14] catalysis. Peroxides were synthesized in high yields by the peroxidation of amines, amides, and lactams catalyzed by ruthenium salts.[15]

Hydroxylation reactions of β-dicarbonyl compounds at the α position, which are related to the peroxidation discovered in the present study, were extensively studied in the past two decades. Generally, the oxidation was carried out with the use of peracids,[16] dimethyldioxirane,[17] hydrogen peroxide,[18] or oxygen.[19] In the studies with the use of oxygen, the formation of peroxide compounds was observed in the following cases: the oxidation of ring-containing β-diketones by singlet oxygen,[19a] reactions with the use of the $CeCl_3/O_2$ system,[19b] and reactions of nitrogen-containing heterocyclic compounds bearing a β-dicarbonyl fragment with the $Mn(OAc)_2/O_2$ system[19c]

Results and Discussion

In the present study, we found that the transition metal (Cu, Co, Mn, Fe)/*tert*-butyl hydroperoxide system can be used for the peroxidation of β-dicarbonyl compounds at the α position. The peroxidation of β-dicarbonyl compounds occurs with high selectivity, does not require the use of a substantial excess of the reactants, and is easily scaled. α-Substituted β-keto esters **1a**−**f**, β-diketones **2a,b,d,e,g,h**, and β-diesters **3a,e,f,h** were used as the starting compounds for the synthesis of target peroxides **4a**−**f**, **5a,b,d,e,g,h**, and **6a,e,f,h** (Scheme 1).

In the context of this peroxidation reaction, it should be noted that in the past decade β-dicarbonyl compounds have found use in oxidative coupling with alkanes, alkenes, amines,

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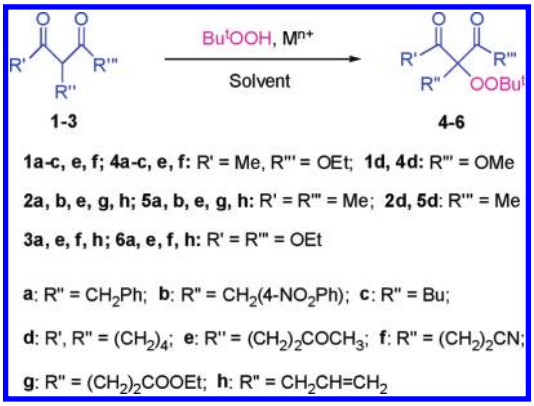
SCHEME 1. Synthesis of α-*tert*-Butylperoxy-β-dicarbonyl Compounds 4−6



esters, and compounds containing the benzyl group.[20] In some studies, the coupling reactions were carried out with the use of *tert*-butyl hydroperoxide,[20b−d] bis(*tert*-butyl) peroxide,[20d] or *tert*-butyl perbenzoate[20d,e] as oxidants in the presence of catalytic amounts of transition metal (Cu, Fe, Co) salts. As a result of the high selectivity of these reactions, the formation of peroxides of β-dicarbonyl compounds was observed in none of the studies. In this context, the coupling of β-dicarbonyl compounds with *tert*-butyl hydroperoxide that acts simultaneously as the oxidant and the second reaction component was unexpected.

The present study was performed in several steps. First, we examined the possibility of performing the peroxidation of these compounds by investigating the reactions of α-benzyl-substituted derivatives of acetoacetic ester **1a**, acetylacetone **2a**, and malonic ester **3a** and optimized the reaction conditions (the reagent ratio, the nature of the catalyst, and the solvent). Then we synthesized a series of asymmetric peroxides with the aim of evaluating the scope of the reaction and preparing the previously unknown compounds.

We chose α-benzylacetoacetic ester **1a** as one of the main reactants for the optimization of the conditions of peroxidation. This reactant contains two centers, CH and $PhCH_2$, active in oxidative reactions (Table 1). The reaction of ester **1a** with *tert*-butyl hydroperoxide afforded α-benzyl-α-*tert*-butylperoxyacetoacetic ester **4a**.

The reactions were performed with the copper salts $Cu(OAc)_2 \cdot H_2O$, $Cu(ClO_4)_2 \cdot 6H_2O$, $Cu(BF_4)_2 \cdot 6H_2O$, $Cu(acac)_2$, CuCl, $CuCl_2 \cdot 2H_2O$, and $CuSO_4 \cdot 5H_2O$ (entries 1−23), the manganese salt $Mn(OAc)_2 \cdot 4H_2O$ (entry 24), and the iron salts $FeCl_3$ and $Fe(acac)_3$ (entries 25 and 26). In all of the reactions presented in Table 1, the peroxidation occurred selectively at the CH fragment, whereas the benzyl CH_2 fragment remained intact.

According to entries 1−4, acetonitrile proved to be the solvent of choice for the peroxidation; neither acetic acid nor ethanol are suitable for this purpose.

In entries 5−10, we evaluated the effect of the amount of the catalyst $Cu(OAc)_2 \cdot H_2O$ (varied from 0.05 to 0.2 mol of the catalyst per mole of **1a**) and the order of its addition on the conversion and the yield of the target peroxide **4a**. The best result was obtained under the conditions when one additional portion of the catalyst and *tert*-butyl hydroperoxide was added 30 min after the beginning of the reaction (entries 8 and 10). In these reactions, we achieved conversions of 94% and 85% and obtained compound **4a** in 48% and 67% yield, respectively (with respect to the reactant used). Apparently, the repeated addition of the catalyst and *tert*-butyl hydroperoxide leads to a decrease in their consumption in side reactions.

Since we failed to achieve the complete conversion of diketone **1a** and a high yield of **4a** in the reactions catalyzed by $Cu(OAc)_2 \cdot H_2O$, the subsequent experiments (entries 11−18) were performed with the use of other salts, such as $Cu(ClO_4)_2 \cdot 6H_2O$ and $Cu(BF_4)_2 \cdot 6H_2O$ (with the strong electron-withdrawing anion). In the reaction catalyzed by $Cu(ClO_4)_2 \cdot 6H_2O$, the complete conversion of dicarbonyl compound **1a** was observed, and the target peroxide **4a** was prepared in 90% yield (entries 13 and 14). Application of dry Bu^{t}OOH practically has no effect on the yield of the peroxide **4a** (entry 14, footnote d). The experiment with the use of $Cu(BF_4)_2 \cdot 6H_2O$ (entry 18) also gave a good result (yield of **4a** was 79%). In the reactions catalyzed by the copper salts $Cu(acac)_2$, CuCl, $CuCl_2 \cdot 2H_2O$, and $CuSO_4 \cdot 5H_2O$ (entries 19−23), the manganese salt $Mn(OAc)_2 \cdot 4H_2O$ (entry 24), and the iron salts $FeCl_3$, $Fe(acac)_3$ (entries 25 and 26), we did not obtain satisfactory results.

In addition to the experimental results presented in Table 1, we carried out reactions with the use of the salts $Co(OAc)_2$, $Co(ClO_4)_2 \cdot 6H_2O$, $Co(acac)_2$, $CoCl_2 \cdot 6H_2O$, $H_7[P(Mo_2O_7)_6] \cdot nH_2O$, and $RuCl_3 \cdot nH_2O$ as the catalysts under the conditions of the best experiment (entry 13). In the presence of Co-containing catalysts, peroxide **4a** was obtained only in trace amounts. The reactions catalyzed by Mo- or Ru-containing compounds did not afford **4a** at all. The formation of peroxide **4a** was not observed also in the reactions catalyzed by main-group metal perchlorates ($MgClO_4$ and $KClO_4$).

α-Benzylacetylacetone **2a** (the structural analogue of keto ester **1a**) was also used for the optimization of the peroxidation with *tert*-butyl hydroperoxide. In this case, we obtained α-benzyl-α-*tert*-butylperoxyacetylacetone **5a** (Table 2).

In this case, as in the peroxidation of keto ester **1a** (Table 1), the copper salts $Cu(ClO_4)_2$ and $Cu(BF_4)_2$ proved to be the catalysts of choice (entries 2−8). In these reactions, the complete conversion of **2a** was achieved, and α-benzyl-α-*tert*-butylperoxyacetylacetone **5a** was obtained in 73% (entry 6) and 69% (entry 8) yields. The main difference of the peroxidation of diketone **2a** from that of keto ester **1a** is that the cobalt salts $CoCl_2 \cdot 6H_2O$, $Co(acac)_2$, and $Co(ClO_4)_2 \cdot 6H_2O$ can also catalyze the peroxidation (entries 10−12). The iron salts $Fe(acac)_3$ and $FeCl_3$ (entries 13 and 14) and the manganese salt $Mn(OAc)_2 \cdot 4H_2O$ (entry 15) are ineffective as the catalysts.

In addition to the experiments presented in Table 2, we tested the catalysts $H_7[P(Mo_2O_7)_6] \cdot nH_2O$ and $RuCl_3 \cdot nH_2O$ under the optimized conditions (see entry 5). These catalysts proved to be ineffective in the peroxidation of diketone **2a**.

On the whole, diketone **2a** is characterized by higher reactivity compared to keto ester **1a**. The peroxidation of **2a** can be performed with the use of a wide range of metal salts and, under analogous reaction conditions, the complete conversion of **2a** is achieved 2−4 times faster compared to **1a**.

Diethyl α-benzylmalonate **3a** (the structural analogue of **1a** and **2a**) was used as the third starting compound for the optimization of the conditions of peroxidation. The reaction of this

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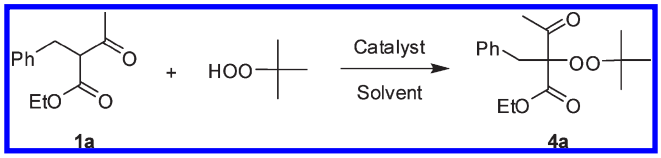
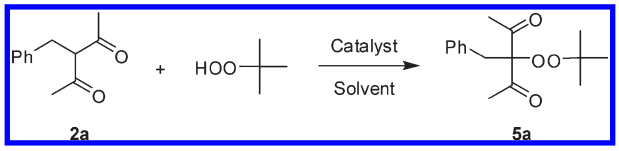
TABLE 1. Transition Metal Salt Catalyzed Peroxidation of α-Benzylacetoacetic Ester 1a with *tert*-Butyl Hydroperoxide[a]



entry	moles *t*-BuOOH per mole **1a**	catalyst	moles catalyst per mole **1a**	reaction time, h	solvent	conv of **1a**, %	yield of **4a**, %
1	2	$Cu(OAc)_2 \cdot H_2O$	0.05	1	CH_3CN	67	62
2	2	$Cu(OAc)_2 \cdot H_2O$	0.05	2	CH_3CN	75	52
3	2	$Cu(OAc)_2 \cdot H_2O$	0.05	1	EtOH	trace	0
4	2	$Cu(OAc)_2 \cdot H_2O$	0.05	1	CH_3COOH	trace	0
5	2	$Cu(OAc)_2 \cdot H_2O$	0.1	1	CH_3CN	71	60
6	3	$Cu(OAc)_2 \cdot H_2O$	0.1	2	CH_3CN	77	50
7	5	$Cu(OAc)_2 \cdot H_2O$	0.1	2	CH_3CN	52	38
8[b]	2 × 2	$Cu(OAc)_2 \cdot H_2O$	2 × 0.05	2 × 1	CH_3CN	94	48
9	2	$Cu(OAc)_2 \cdot H_2O$	0.2	3	CH_3CN	85	33
10[b]	2 × 2	$Cu(OAc)_2 \cdot H_2O$	2 × 0.1	2 × 0.5	CH_3CN	85	67
11	2	$Cu(ClO_4)_2 \cdot 6H_2O$	0.05	1	CH_3CN	100	87
12	2	$Cu(ClO_4)_2 \cdot 6H_2O$	0.1	0.5	CH_3CN	83	76
13	2	$Cu(ClO_4)_2 \cdot 6H_2O$	0.1	1	CH_3CN	100	90 (88)[c]
14	3	$Cu(ClO_4)_2 \cdot 6H_2O$	0.1	1	CH_3CN	100	90 (87)[d]
15	2	$Cu(ClO_4)_2 \cdot 6H_2O$	0.2	1	CH_3CN	100	74
16	2	$Cu(ClO_4)_2 \cdot 6H_2O$	0.1	1	EtOH	trace	0
17	2	$Cu(ClO_4)_2 \cdot 6H_2O$	0.1	1	CH_3COOH	trace	0
18	2	$Cu(BF_4)_2 \cdot 6H_2O$	0.1	1	CH_3CN	100	79
19	2	$Cu(acac)_2$	0.1	1	CH_3CN	60	40
20	2	CuCl	0.1	1	CH_3CN	trace	trace
21	2	$CuCl_2 \cdot 2H_2O$	0.1	1	CH_3CN	16	trace
22	2	$CuSO_4 \cdot 5H_2O$	0.05	1	CH_3CN/H_2O (4:1)	43	41
23	2	$CuSO_4 \cdot 5H_2O$	0.1	1	CH_3CN/H_2O (4:1)	42	14
24	2	$Mn(OAc)_2 \cdot 4H_2O$	0.1	1	CH_3CN	33	21
25	2	$FeCl_3$	0.1	1	CH_3CN	50	24
26	2	$Fe(acac)_3$	0.1	1	CH_3CN	10	trace

[a]General reaction conditions. The catalyst (0.05−0.2 mol per mole of **1a**) and a 70% aqueous Bu^{t}OOH solution (2−5 mol per mole of **1a**) were added to a solution of keto ester **1a** (0.3 g, 1.36 mmol) in the solvent (CH_3CN, EtOH, or CH_3COOH) (5 mL). The reaction mixture was refluxed for 0.5−2 h (at a temperature from 79 to 119 °C). [b]The catalyst $Cu(OAc)_2 \cdot H_2O$ and a 70% aqueous Bu^{t}OOH solution were added to the reaction mixture in two portions. The first portion was added in the beginning of the experiment, and another portion was added 1 h (entry 8) or 30 min (entry 10) after the beginning of the reaction. [c]The experiment was carried out under argon. [d]The experiment was carried out with the use of dry Bu^{t}OOH.

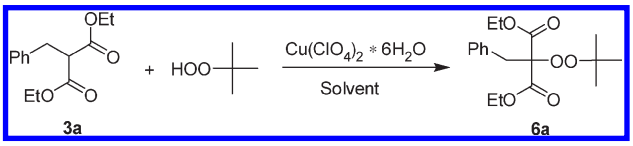
TABLE 2. Transition Metal Salt Catalyzed Peroxidation of α-Benzylacetylacetone 2a with *tert*-Butyl Hydroperoxide[a]



entry	moles *t*-BuOOH per mole **2a**	catalyst	τ, h	conv of **2a**, %	yield of **5a**, %
1	2	$Cu(OAc)_2 \cdot H_2O$	1	87	34
2[b]	2	$Cu(ClO_4)_2 \cdot 6H_2O$	1	87	51
3	2	$Cu(ClO_4)_2 \cdot 6H_2O$	0.5	100	64
4[c]	2	$Cu(ClO_4)_2 \cdot 6H_2O$	0.5	71	32
5	3	$Cu(ClO_4)_2 \cdot 6H_2O$	0.5	100	71
6	3	$Cu(ClO_4)_2 \cdot 6H_2O$	0.25	100	73
7	5	$Cu(ClO_4)_2 \cdot 6H_2O$	0.5	100	52
8	3	$Cu(BF_4)_2 \cdot 6H_2O$	0.5	100	69
9	3	$Cu(acac)_2$	1	38	29
10	3	$CoCl_2 \cdot 6H_2O$	1	100	34
11	3	$Co(acac)_2$	1	98	24
12	3	$Co(ClO_4)_2 \cdot 6H_2O$	1	trace	trace
13	3	$Fe(acac)_3$	1	45	23
14	3	$FeCl_3$	1	73	12
15	2	$Mn(OAc)_2 \cdot 4H_2O$	1	86	15

[a]General reaction conditions. The catalyst (13−30 mg, 0.05 mol per mole of **2a**) and a 70% aqueous Bu^{t}OOH solution (0.41−1.03 g, 2−5 mol per mole of **2a**) were added to a solution of diketone **2a** (0.3 g, 1.58 mmol) in CH_3CN (5 mL). The reaction mixture was refluxed for 0.25−2 h (the temperature of the reaction mixture was 79−81 °C). [b]The reaction was performed with the use of 0.02 mol of $Cu(ClO_4)_2 \cdot 6H_2O$ per mole of **2a**. [c]The temperature of the reaction mixture was 58−60 °C.

TABLE 3. Copper Perchlorate Catalyzed Peroxidation of Diethyl α-Benzylmalonate 3a with *tert*-Butyl Hydroperoxide[a]



entry	moles *t*-BuOOH per mole **3a**	moles catalyst per mole **3a**	reaction time, h	conv of **3a**, %	yield of **6a**, %
1	2	0.1	1	43	32
2	2	0.2	2	62	41
3	5	0.3	1	87	65
4	5	0.3	1.5	99	42
5	3	0.4	1	98	59
6	5	0.4	1	98	67
7	5	0.5	0.5	98	59

[a]General reaction conditions. The catalyst $Cu(ClO_4)_2 \times 6H_2O$ (0.1−0.5 mol per mole of **3a**) and a 70% aqueous Bu^{t}OOH solution (2−5 mol per mole of **3a**) were added to a solution of diester **3a** (0.3 g, 1.2 mmol) in CH_3CN (5 mL). The reaction mixture was refluxed for 0.5−2 h (the temperature of the reaction mixture was 79−81°C).

compound catalyzed by $Cu(ClO_4)_2 \cdot 6H_2O$, which was proved to be the best catalyst for the reactions of keto ester **1a** and diketone **2a** (Table 3), afforded diethyl α-benzyl-α-*tert*-butylmalonate **6a**.

In entries 1−7, it was shown that the virtually complete conversion of diester **3a** can be achieved with the use of a 5-fold molar excess of *tert*-butyl hydroperoxide in the presence of the catalyst (30−50 mol %), which is substantially higher compared to the reactions of keto ester **1a** and diketone **2a**.

Therefore, a comparison of the reactions of three dicarbonyl compounds **1a**, **2a**, and **3a** under analogous conditions showed that the keto ester gave the target peroxide **4a** in the highest yield (90%), the peroxidation of the diketone resulted in a lower yield (**5a**, 73%), whereas the reaction of the diester produced peroxide **6a** in the lowest yield (67%). The complete conversion of diketone **2a** is achieved most rapidly (15 min), whereas 1 h is required for the complete conversion of keto ester **1a** and diester **3a**.

With the aim of evaluating the scope of the peroxidation with respect to other dicarbonyl compounds and preparing previously unknown compounds, we synthesized peroxides **4**−**6** under the optimized reaction conditions (Table 4).

On the basis of the results of the synthesis of structurally different peroxides in 37−90% yields, it could be expected that the above-described method for the peroxidation can be extended to other α-substituted β-dicarbonyl compounds.

Proposed Reaction Mechanism. Taking into account the data published in the literature,[20] it can be suggested that the peroxidation of β-dicarbonyl compounds **I** occurs according to Scheme 2 (as exemplified by the use of copper salts as the catalyst). In step **A**, β-dicarbonyl compound **I** and Cu^{II} give complex **II**, which reacts with the Bu^{t}OO radical (step **B**) to form the target peroxide **III** and Cu^{I}. In step **C**, monovalent copper is oxidized by *tert*-butyl hydroperoxide to give Cu^{II} and the Bu^{t}O radical, which abstracts hydrogen from the *tert*-butyl hydroperoxide molecule (step **D**) to form the Bu^{t}OO radical (or its complex with metal),[10b,11b,21] which is consumed in the step **B**. The Bu^{t}OO radical can also be generated in the process **E**, according to which Cu^{II} (as a salt or complex **II** with a dicarbonyl compound) oxidizes Bu^{t}OOH to the Bu^{t}OO radical (which is consumed in step **B**) to form monovalent copper.[10a,g,14]

The possibility that the reaction occurs through step **B** (the transformation of **II** into **III**) was confirmed experimentally (see Supporting Information). Thus, the copper complex, which was prepared from α-benzylacetylacetone **2a** according to a known method,[22] was subjected to peroxidation, resulting in the formation of peroxide **5a** in 44% yield. This experiment, as well as another experiment with the use of the copper complex of α-benzylacetylacetone in catalytic amounts (5 mol %, the conversion of **2a** was 63%, the yield of **5a** was 23%, see Supporting Information), partially confirmed step **E**, according to which complex **II** oxidizes *tert*-butyl hydroperoxide to the Bu^{t}OO radical.

Apparently, the efficiency of the catalyst $Cu(ClO_4)_2$ (like that of $Cu(BF_4)_2$) in the peroxidation is determined primarily by a combination of three factors. First, copper(II) perchlorate can be involved in the reaction with β-dicarbonyl compounds to form complexes.[23,24] As a result, the reaction mixture contains, in addition to the starting diketone **I** and $Cu(ClO_4)_2$, complex **II**. Second, $Cu(ClO_4)_2$ acts as a strong oxidant in acetonitrile;[25] this salt is a stronger oxidant compared to $Cu(NO_3)_2$ and $CuCl_2$.[26] As a result of this property, $Cu(ClO_4)_2$ rapidly oxidizes *tert*-butyl hydroperoxide to the Bu^{t}OO radical. Third, the efficiency of $Cu(ClO_4)_2$ as the catalyst is manifested in that monovalent copper that is generated (apparently, as $CuClO_4$) in the step **B** readily forms the complex with acetonitrile of composition $CuClO_4 \cdot 4CH_3CN$, [27] which is relatively easily oxidized by *tert*-butyl hydroperoxide to divalent copper (step **C**), thus providing its regeneration.

As for the reaction mechanism of peroxidation, it should be noted that the reactions with unsubstituted acetylacetone, acetoacetic ester, and malonic ester afford complex mixtures of products. This is attributed to the fact that compound **III** containing the hydrogen atom and the Bu^{t}OO group in the

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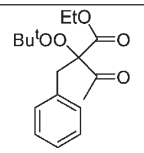
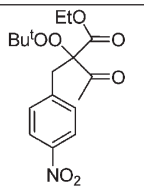
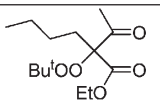
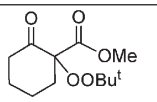
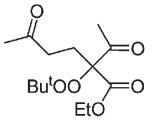
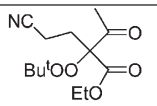
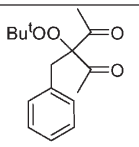
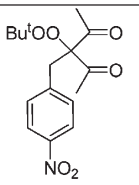
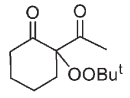
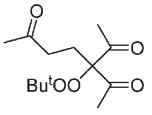
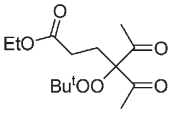
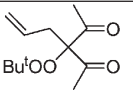
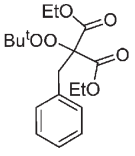
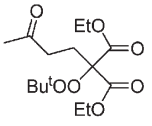
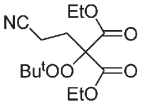
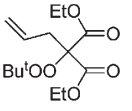
TABLE 4. Structures and Yields of Peroxides 4−6 Derived from β-Dicarbonyl Compounds 1−3

Structures of peroxides **4-6**, yields, %			
 **4a** [a], 90 (89) [d]	 **4b** [a], 53	 **4c** [a], 78	 **4d** [a], 45
 **4e** [a], 58	 **4f** [a], 66	 **5a** [b], 73	 **5b** [b], 46
 **5d** [b], 61	 **5e** [b], 51	 **5g** [b], 75 (74) [d]	 **5h** [b], 57
 **6a** [c], 67	 **6c** [c], 37	 **6f** [c], 51	 **6h** [c], 52

[a]A 70% aqueous Bu^{t}OOH solution (2 mol per mole of **1**) was added to a solution of ethyl 2-substituted-3-oxobutanoates **1** (0.3 g) and $Cu(ClO_4)_2 \cdot 6H_2O$ (0.1 mol per mole of **1**) in CH_3CN (5 mL). The reaction mixture was refluxed at 79−81 °C for 1 h. [b]A 70% aqueous Bu^{t}OOH solution (3 mol per mole of **2**) was added to a solution of 3-substituted-2,4-dione **2** (0.3 g) and catalyst $Cu(ClO_4)_2 \cdot 6H_2O$ (0.05 mol per mole of **2**) in CH_3CN (5 mL). The reaction mixture was refluxed at 79−81 °C for 15 min. [c]A 70% aqueous Bu^{t}OOH solution (5 mol per mole of **3**) was added to a solution of diethyl 2-substituted malonate **3** (0.3 g) and catalyst $Cu(ClO_4)_2 \cdot 6H_2O$ (0.4 mol per mole of **3**) in CH_3CN (5 mL). The reaction mixture was refluxed at 79−81 °C for 1 h. [d]The experiments on the synthesis of **4a** and **5g** were scaled up to 10 times larger amounts of the reactants.

α position apparently gives complex **II** (R = Bu^{t}OO) containing the unstable vinyl peroxide moiety, as well as to the fact that the second Bu^{t}OO group can be incorporated into the molecule to form diperoxides unstable under the reaction conditions.

It is possible that the target peroxides are generated in insignificant amounts according to the mechanism of recombination of the following radicals: the Bu^{t}OO radical (or its complex with metal) and the C-centered radical, which is formed through the abstraction of hydrogen from the α-CH fragment of β-dicarbonyl compounds by the Bu^{t}OO and Bu^{t}O radicals[9a,10d,11b,13,28] or through the oxidation of the dicarbonyl compounds by metal ions.[29] However, the recombination of the radicals is unlikely because the dimers of dicarbonyl compounds, which are generally formed by the radical coupling of two C-centered radicals, were not detected,[30] and the peroxidation of α-allylacetylacetone **2h** was not accompanied by its oligomerization. In the experiment on the peroxidation of α-benzylacetoacetic ester **1a** in the presence of a 5-fold molar excess of allyl acetate, the formation of the product of the radical addition at the C=C bond was not observed; the target peroxide **4a** was obtained in 86% yield (the experiment is described in Supporting Information). It should be noted that the radical addition of ketones to compounds containing the double bond are well-known and are typical of C-centered radicals generated from ketones.[31]

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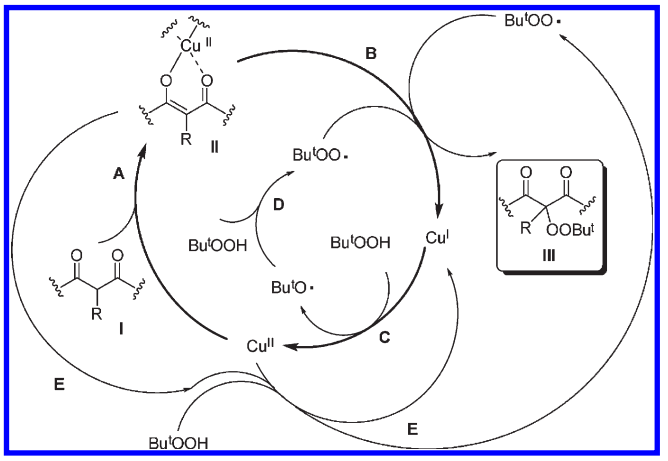
SCHEME 2. Proposed Reaction Mechanism of Peroxidation of β-Dicarbonyl Compounds Exemplified by the Use of Copper Salts As the Catalyst



Establishment of the Structures of the Peroxides. Peroxides **4a**−**c**,**e**−**f**, **5b**,**d**,**e**,**g**,**h**, and **6e**,**g**,**h** are liquids. Peroxides **4d**, **5a**, **b**, and **6a** are solid compounds with mp varying from 34 to 36 °C (**5a**) to 109−110 °C (**5b**). The structures of these compounds were established by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The ^{13}C NMR spectra show characteristic signals for the carbon atoms of the $COOC(CH_3)_3$ fragment at δ 85.41−97.16, 80.37− 81.79, and 26.19−26.69. The retention of the characteristic signals of the C=O group at δ 165.86−206.92 is important evidence that this group remains intact in the reaction with *tert*-butyl hydroperoxide. In the ^{1}H NMR spectra, the absence of the signal for the hydrogen atom of the α-CH fragment and the presence of the signals of the CH_3CO (δ 1.89− 2.24) and $C(CH_3)_3$ (δ 1.23− 1.33) groups are the most characteristic data.

A reliable proof of the structures of organic peroxides, even despite the NMR spectroscopic and elemental analysis data, is generally a difficult problem. Hence, to determine with certainty the structures of the peroxides, the structure of compound **5b** was established by X-ray diffraction study (the molecular structure of **5b** is shown in Supporting Information), which confirmed the structures of these compounds.

Conclusion

Transition metal (Cu, Fe, Mn, Co) salts were found to catalyze the peroxidation of α-substituted β-dicarbonyl compounds at the α position by *tert*-butyl hydroperoxide. On the basis of this reaction, we developed a selective and experimentally convenient method for the synthesis of α-*tert*-butylperoxy-β-dicarbonyl compounds. The synthesis is easily scaled without a decrease in the yield of the target peroxides, which can be prepared in gram amounts. The reactions are performed in acetonitrile with the use of 5−40 mol % of the catalyst ($Cu(ClO_4)_2$ is the catalyst of choice) and an aqueous solution of *tert*-butyl hydroperoxide (2−3 mol per mole of a β-dicarbonyl compound). The reaction is suitable for structurally different α-substituted β-dicarbonyl compounds. The target peroxides are obtained in the highest yields (up to 90%) from β-keto esters and in somewhat lower yields from β-diketones (up to 75%) and malonates (up to 69%).

Experimental Section

Caution: Although we have encountered no difficulties in working with peroxides, precautions, such as the use of shields, fume hoods, and the avoidance of transition metal salts, heating, and shaking, should be taken whenever possible.

Synthesis of Ethyl 2-Benzyl-2-(*tert*-butylperoxy)-3-oxobutanoate 4a (entry 13, Table 1). A 70% aqueous Bu^{t}OOH solution (0.35 g, 2.72 mmol, 2 mol per mole of **1a**) was added to a solution of 2-benzyl-3-oxobutanoate **1a** (0.3 g, 1.36 mmol) and $Cu(ClO_4)_2\cdot 6H_2O$ (0.05 g, 0.136 mmol, 0.1 mol per mole of **1a**) in CH_3CN (5 mL). The reaction mixture was refluxed at 79−81 °C for 1 h, cooled to 20−25 °C, poured into water (40 mL), stirred, and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with water (3 × 10 mL), dried over Na_2SO_4, and filtered. The filtrate was evaporated using a water-jet vacuum pump. The residue was chromatographed using a petroleum ether−ethyl acetate system with an increase in the fraction of the latter solvent from 0 to 20%. Product **4a** was obtained in 90% yield (0.38 g, 1.23 mmol). Colorless oil. R_f = 0.68 (TLC, hexane−ethyl acetate, 5:1). ^{1}H NMR (300.13 MHz, $CDCl_3$), δ: 1.21 (t, 3H, J = 7.3 Hz), 1.30 (s, 9H), 1.89 (s, 3H), 3.44 (dd, 2H, J = 13.9, 69.7 Hz), 4.10−4.23 (m, 2H), 7.16−7.26 (m, 5H). ^{13}C NMR (75.48 MHz, $CDCl_3$), δ: 13.8, 26.5, 27.0, 37.1, 61.5, 81.0, 92.6, 126.6, 127.9, 130.6, 134.9, 167.5, 203.4. Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.32; H, 7.89.

Synthesis of 3-Benzyl-3-(*tert*-butylperoxy)pentane-2,4-dione 5a (entry 6, Table 2). A 70% aqueous Bu^{t}OOH solution (0.61 g, 4.74 mmol, 3 mol per mole of **2a**) was added to a solution of 3-benzylpentane-2,4-dione **2a** (0.3 g, 1.58 mmol) and $Cu(ClO_4)_2\cdot 6H_2O$ (0.03 g, 0.08 mmol, 0.05 mol per mole of **2a**) in CH_3CN (5 mL). The reaction mixture was refluxed at 79−81 °C for 15 min, cooled to 20−25 °C, poured into water (40 mL), stirred, and extracted with CH_2Cl_2 (3 × 10 mL). The isolation was carried out as described in entry 13, Table 1. Product **5a** was obtained in 73% yield (0.32 g, 1.15 mmol). Yellowish crystals. Mp = 34−36 °C. R_f = 0.74 (TLC, hexane−ethyl acetate, 10:1). ^{1}H NMR (300.13 MHz, $CDCl_3$), δ: 1.33 (s, 9H), 1.98 (s, 6H), 3.36 (s, 2H), 7.14−7.27 (m, 5H). ^{13}C NMR (75.48 MHz, $CDCl_3$), δ: 26.6, 27.2, 37.1, 81.3, 97.0, 126.7, 128.0, 130.5, 135.0, 203.3. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.10; H, 7.94.

Synthesis of Diethyl 2-Benzyl-2-(*tert*-butylperoxy)malonate 6a (entry 6, Table 3). A 70% aqueous Bu^{t}OOH solution (0.77 g, 6 mmol, 5 mol per mole of **3a**) was added to a solution of diethyl 2-benzylmalonate **3a** (0.3 g, 1.2 mmol) and $Cu(ClO_4)_2\cdot 6H_2O$ (0.178 g, 0.48 mmol, 0.4 mol per mole of **3a**) in CH_3CN (5 mL). The reaction mixture was refluxed at 79−81 °C for 1 h, cooled to 20−25 °C, poured into water (40 mL), stirred, and extracted with CH_2Cl_2 (3 × 10 mL). The isolation was carried out as described in entry 13, Table 1. Product **6a** was obtained in 67% yield (0.27 g, 0.8 mmol). White crystals. Mp = 44−45 °C. R_f = 0.37 (TLC, hexane−ethyl acetate, 10:1). ^{1}H NMR (300.13 MHz, $CDCl_3$), δ: 1.20 (t, 6H, J = 7.3 Hz), 1.29 (s, 9H), 3.50 (s, 2H), 4.11−4.21 (m, 4H), 7.14−7.28 (m, 5H). ^{13}C NMR (75.48 MHz, $CDCl_3$), δ: 13.9, 26.5, 37.8, 61.6, 81.0, 87.9, 126.8, 127.9, 130.3, 134.9, 166.9. Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74. Found: C, 63.76; H, 7.84.

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Supporting Information Available: Experimental procedures for the synthesis of **4a**−**f**, **5a**,**b**,**d**,**e**,**g**,**h**, and **6a**,**e**,**f**,**h**, their ^{1}H and ^{13}C NMR spectra, and details of X-ray data for **5b**, including CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.