



Synthesis of α -ester– β -keto peroxides via iron-catalyzed carbonylation–peroxidation of α,β -unsaturated esters

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ABSTRACT

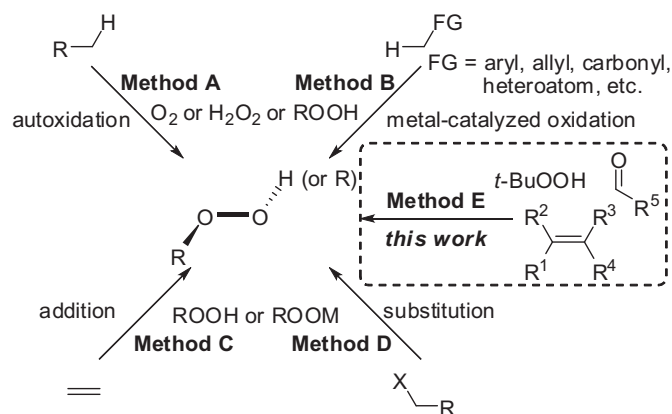
A general and practical method for the synthesis of α -ester– β -keto peroxides has been achieved by iron-catalyzed three-component reactions of alkenes, aldehydes, and TBHP. A wide variety of functionalized organic peroxides were synthesized efficiently and selectively.

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1. Introduction

Organic peroxides have received considerable attention in pharmacy, biochemistry and food chemistry because of their close relationship with drug design, cell damage, and food safety.¹ Organic peroxides also play as key reactive intermediates in synthetic chemistry.² Hydroperoxides and cycloperoxides are typically obtained by the radical processes in the presence of O₂ or H₂O₂ (Scheme 1, Method A).³ Kharasch and co-workers were the pioneers to introduce peroxy into organic molecules by the use of hydroperoxides in the presence of various transition-metal catalysts.⁴ Since these pioneering works, this strategy has been developed as an efficient and powerful method for peroxidation (Scheme 1, Method B).⁵ In addition, the addition of peroxy radicals to alkenes (Scheme 1, Method C) and the base-catalyzed nucleophilic reactions of hydroperoxides with various electrophiles (Scheme 1, Method D) were also developed to generate the mixed peroxides.⁶ However, the established methods have more-limited scope. Therefore, new peroxidation methods are highly desirable and valuable. Recently, we reported an iron-catalyzed three-component carbonylation–peroxidation reaction of alkene, aldehyde and hydroperoxide.⁷ The methodology allows a carbonyl group⁸ and a peroxy group to add across C=C bonds of styrene derivatives selectively.⁹ The generated mixed peroxides could be

efficiently and selectively transformed into multisubstituted α -carbonyl epoxides in the presence of a base catalyst.⁷ These preliminary results prompt us to further investigate iron-catalyzed three-component reactions of α,β -unsaturated esters, aldehydes, and *tert*-butyl hydroperoxide (TBHP). The study highlights that the densely functionalized peroxides, α -ester– β -keto peroxides, which are difficult to be obtained through the conventional methods, were efficiently and selectively built up from three-component assembling (Scheme 1, Method E).



Scheme 1. General methods for synthesis of organic peroxides.

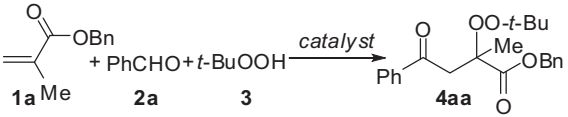
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2. Results and discussion

2.1. Optimization of the reaction conditions

The reaction of benzyl methacrylate (**1a**) with benzaldehyde (**2a**) and TBHP (**3**) was chosen to establish the suitable reaction conditions (Table 1). The yields of the desired carbonylation–peroxidation product **4aa** were substantially improved through increasing the amount of **2a** and **3** (entries 1–4). It is worth noting that **4aa** was obtained in the absence of catalyst, albeit in 31% yield (41% for 6 h) (entry 5). Furthermore, the catalyst screening with various iron sources (entries 6–13) as well as other metal salts (entries 14–17) indicated FeCl₂ as the best catalyst for the transformation.¹⁰ To our satisfied, an excellent result was obtained using 4.0 equiv of TBHP (**3**) in CH₃CN at 85 °C (91%, entry 18).

Table 1
Optimization of the reaction conditions^a



Entry	2a (equiv)	3 (equiv)	Catalyst (2.5 mol %)	4aa yield (%) ^b
1	1	1	FeCl ₂	10
2	1	3	FeCl ₂	28
3	3	3	FeCl ₂	74
4	5	3	FeCl ₂	82
5	5	3	—	31(41) ^c
6	5	3	FeCl ₃	73
7	5	3	Fe(OAc) ₂	68
8	5	3	Fe ₂ (CO) ₉	70
9	5	3	FeBr ₂	56
10	5	3	FeCl ₃ ·6H ₂ O	50
11	5	3	FeSO ₄ ·7H ₂ O	41
12	5	3	Fe(acac) ₂	30
13	5	3	Fe(acac) ₃	40
14	5	3	CuCl	72
15	5	3	CuBr ₂	49
16	5	3	CoCl ₂	52
17	5	3	Mn(OAc) ₂	74
18	5	4	FeCl ₂	91

^a Conditions: **1a** (0.5 mmol), catalyst (2.5 mol %), MeCN (3 mL), 85 °C, 1 h, under nitrogen atmosphere.

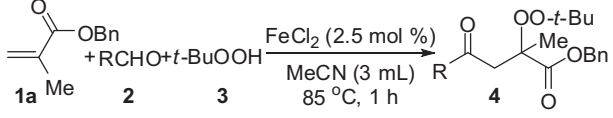
^b Reported yields were based on **1a** and determined by ¹H NMR using an internal standard.

^c 6 h.

2.2. The scope of aldehydes

With the optimized conditions in hand, the scope of aldehydes (**2**) was investigated by the use of **1a** as a model substrate (Table 2). Both aromatic and aliphatic aldehydes were successfully applied to the present transformation. Electron-donating substituted benzaldehydes (**2b** and **2c**) afforded the desired peroxides in excellent yields (entries 1 and 2), while benzaldehydes with electron-withdrawing group (**2d–f**) retarded the efficiency of the transformation (entries 3–5). Heteroaromatic aldehydes (**2g–i**) also led to the corresponding peroxides (entries 6–8). 1-Naphthaldehyde (**2j**) showed a lower efficiency due to the steric effect (entry 9). Aliphatic aldehydes could also be used to give the desired peroxides under the standard conditions (entries 10–12). Importantly, the reactions of formamides (**2n** and **2o**) with **1a** led to the expected peroxides, albeit with the use of large excess amount of formamides in the absence of MeCN (entries 13–14). Interestingly, the decarbonylation product (**5**) instead of the desired carbonylation–peroxidation product was obtained quantitatively when pivaldehyde **2p** was applied under the standard conditions (Eq. 1).

Table 2
The scope of aldehydes^a

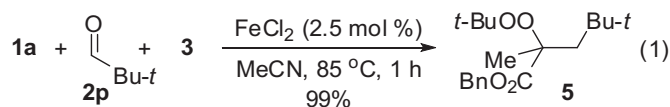


Entry	2	4	Yield(%) ^b
1		2b → 4ab	89(75)
2		2c → 4ac	92(78)
3		2d → 4ad	80(72)
4		2e → 4ae	70(58)
5		2f → 4af	55(46)
6		2g → 4ag	73(63)
7		2h → 4ah	66(56)
8		2i → 4ai	55(45)
9		2j → 4aj	27(13)
10		2k → 4ak	73(72)
11		2l → 4al	58(46)
12		2m → 4am	84(80)
13		2n → 4an	60(45) ^c
14		2o → 4ao	57(51) ^c

^a Conditions: **1a** (0.5 mmol), 85 °C, 1 h, under nitrogen atmosphere.

^b Reported yields were based on **1a** and determined by ¹H NMR using an internal standard; isolated yields were given in parentheses.

^c **2k** (10 mmol); without MeCN.



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