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General Metal-Free Baeyer–Villiger-Type Synthesis of Vinyl Acetates

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ABSTRACT

Oxone, a cheap, stable, and nonhazardous oxidizing reagent, transforms α,β-unsaturated ketones of defined stereochemistry into their corresponding vinyl acetates through a Baeyer–Villiger reaction. This process is general and straightforward, tolerating a wide range of functional groups.

Vinyl acetates are significant compounds for industry, as they are building blocks in the manufacturing of polymers (polyvinyls). Although vinyl acetate itself is commercially available, the preparation of other more elaborated derivatives is a challenging synthetic task. Traditionally, this family of compounds is accessed employing either of the transition-metal-based methodologies available: the addition of carboxylic acids to terminal alkynes, catalyzed by different ruthenium[1] or rhenium complexes;[2] the palladium-catalyzed vinylation of organic halides;[3] or the usage of chromium carbene complexes.[4] Such preparations imply working with expensive and elaborated catalysts and lack generality, with substituted vinyl acetate products being rendered as undesired mixtures of (*E*)- and (*Z*)-isomers. In this communication, we disclose a general transition-metal-free synthesis of diastereopure vinyl acetates, prepared by the Baeyer–Villiger oxidation reaction[5] of α,β-unsaturated methylketones with Oxone (potassium monopersulfate triple salt, $KHSO_5 \cdot 1/2\ KHSO_4 \cdot 1/2\ K_2SO_4$, Dupont registered name).[6]

This work was not originally intended and resulted from our long-term research program, where we explored the chances of carrying out a facile multigram oxidation of α,β-unsaturarted methylketones **1**, to the corresponding epoxides **2**,[7] with the latter to be tested as substrates for our proline/guanidinium salt organocatalytic systems.[8] Commercially available (*E*)-4-phenyl-3-buten-2-one, **1a**, was adopted as a model substrate and was reacted with a range of standard oxidizing agents, at room temperature,

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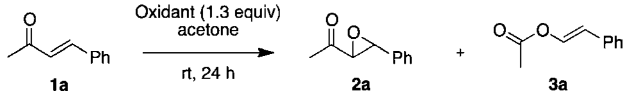
Table 1. Initial Screening of Reagents for the Oxidation Reaction of α,*β*-Unsaturated Ketone **1a**[a]



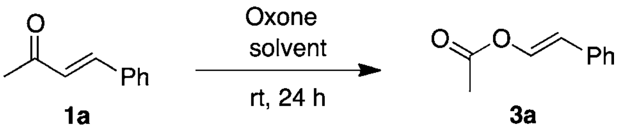
entry	oxidant	conversion[b]	conversion[c]
1	*m*CPBA	9	18
2	$Ca(ClO)_2$	–	–
3	H_2O_2·urea	–	–
4[d]	H_2O_2	–	–
5[e]	*t*-BuOOH	–	–
6	Oxone	–	9

[a] General reaction conditions: α,*β*-unsaturated ketone **1a** (1 equiv), oxidant (1.3 equiv), in acetone (0.5 M), 24 h, at room temperature. [b] Conversion percentage of ketone **1a** to epoxide **2a**, as determined by ^{1}H NMR spectroscopy on crude reaction mixtures. [c] Conversion percentage of ketone **1a** to acetate **3a**, as determined by ^{1}H NMR spectroscopy on crude reaction mixtures. [d] H_2O_2 30% weight in water. [e] *t*-BuOOH was used as a 5.0 M solution in decane.

employing acetone as solvent (Table 1). The reaction mixtures were worked up and analyzed by ^{1}H NMR spectroscopy. *m*-Chloroperbenzoic acid (*m*CPBA) converted ketone **1a** to a mixture consisting of epoxide **2a** (9%) and the Baeyer–Villiger oxidation product vinyl acetate **3a** (18%), amid a complex reaction mixture (Table 1, entry 1). While $Ca(ClO)_2$, H_2O_2, or *t*-BuOOH did not react with the α,*β*-unsaturated ketone (Table 1, entries 2–5), Oxone rendered the vinyl acetate **3a** in low conversion, although no side products were spotted in the reaction media (Table 1, entry 6). In the interest of preparing configurationally stable vinyl acetate products such as **3a**, to our knowledge, this Baeyer–Villiger reaction of Oxone had no precedents in the literature and was worth studying. It is relevant to remark that Oxone is a crystalline solid oxidant, easy to handle, nontoxic or hazardous, soluble in water, and, above all, stable and cheap.[9]

To improve the Oxone-promoted oxidation of α,*β*-unsaturated ketone **1a** to its corresponding vinyl acetate **3a**, outlined in Table 1, different reaction conditions were explored (Table 2). With acetone as the solvent, a rise in the number of equivalents of the oxidant from 1.3 to 1.5 did not improve the reaction significantly (Table 2, entries 1 and 2). Accordingly, the effect of using either of a collection of organic solvents, all of them previously used in other Oxone-promoted reactions, was investigated. The results obtained for CH_3CN/H_2O and *N*,*N*-dimethylformamide (DMF) were comparable in terms of crude conversion of ketone **1a** to acetate **3a** (Table 2, entries 3 and 4). Alternatively, a mixture of CH_2Cl_2/H_2O, or neat EtOH, was observed to be inappropriate as solvents for this reaction (Table 2, entries 5 and 6). Full conversion of ketone **1a** to styryl acetate **3a** was obtained in 24 h, using DMF and a 2-fold excess of Oxone, under heterogeneous reaction conditions (Table 2, entry 8). Product **3a** was unambiguosly characterized as (*E*)-styryl acetate by ^{1}H NMR spectroscopy, from comparison of the value of the $^3J_{H-H}$ coupling constants for the olefinic protons of this material with those previously reported in the literature [(*E*)-isomer: $^3J_{trans}$ = 12.8 Hz; (*Z*)-isomer: $^3J_{cis}$ = 7.4 Hz].[1h]

Table 2. Screening of Reaction Conditions for the Oxone-Promoted Oxidation of α,*β*-Unsaturated Ketone **1a** to Vinyl Acetate **3a**[a]



entry	equiv Oxone	solvent	conversion[b]
1	1.3	acetone	9
2	1.5	acetone	13
3	1.5	CH_3CN/H_2O (10:1)	77
4	1.5	DMF	83
5	1.5	CH_2Cl_2/H_2O (10:1)	0
6	1.5	EtOH	–[c]
7	2	CH_3CN/H_2O (10:1)	92
8	2	DMF	96

[a] General reaction conditions: α,*β*-unsaturated ketone **1a** (1 equiv), Oxone, solvent (0.5 M), 24 h, at room temperature. [b] Conversion percentage of ketone **1a** to vinyl acetate **3a**, as determined by ^{1}H NMR spectroscopy on crude reaction mixtures. [c] Product **3a** was detected by ^{1}H NMR spectroscopy amid a complex reaction mixture.

To study the stereoelectronic factors involved in our oxidation reaction a selection of α,*β*-unsaturated methylketones **1a**–**r**, bearing diverse functional groups and substitution patterns, were reacted with an excess of Oxone under our finest reaction conditions (Table 3). Ketones **1b**–**r** were prepared in diastereopure form, (*E*), according to modified literature procedures.[10] Although 2 equiv of Oxone sufficed to convert ketone **1a** to vinyl acetate **3a** (Table 2, entry 8), it was not the case for any other ketone **1b**–**r**. For these substrates a larger excess of the oxidizing reagent was necessary to achieve acceptable conversion values for products **3b**–**r** in a reasonable reaction time.[11] The course of the reactions was carefully followed by TLC, and they were stopped and worked up as soon as the corresponding methylketone **1** was consumed. All the vinyl acetate products **3b**–**r** proved to be fragile in the presence of water, suffering from some hydrolysis of the ester moiety. In order to attain optimum yields of isolated pure products **3**, the DMF was rigorously dried, the reactions were carried out under an inert atmosphere, and aqueous workups were avoided.[12] As evidence of these difficulties, it has to be noted that styryl acetate, **3a**, was isolated in analytically pure form in a maximum yield of 73%

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(9) Oxone was purchased from Aldrich (1 g = \$0.06).

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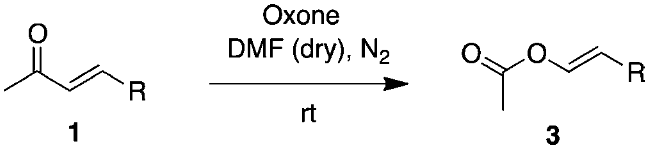
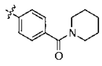
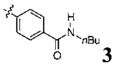
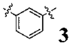
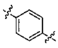
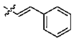
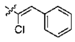
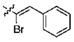
(11) Vinyl acetate products **3** were experienced to degrade within the reaction media after prolonged reaction times.

(12) See Supporting Information for details.

Table 3. Oxone-Promoted Oxidation of α,*β*-Unsaturated Methylketones **1** to Vinyl Acetates **3**[a]



entry	R	Oxone equiv	time (h)[b]	yield %[c]
1	C_6H_5 **3a**	2	24	73
2	4-F-C_6H_4 **3b**	3	21	80
3	4-Cl-C_6H_4 **3c**	3	16	89
4	4-Br-C_6H_4 **3d**	3	17	88
5	3-Cl-C_6H_4 **3e**	5	24	73
6	4-CF_3-C_6H_4 **3f**	5	24	57
7	4-Me-C_6H_4 **3g**	3	24	68
8	4-Et-C_6H_4 **3h**	3	18	92
9	4-CO_2Me-C_6H_4 **3i**	5	24	70
10	 **3j**	3	24	94
11	 **3k**	5	19	80
12	4-CN-C_6H_4 **3l**	5	24	45
13	4-NO_2-C_6H_4 **3m**	5	72	45
14	3-NO_2-C_6H_4 **3n**	5	24	59
15	2-NO_2-C_6H_4 **3o**	5	48	49
16	3-OH-C_6H_4 **3p**	3	14	95
17	1-naphthyl **3q**	3	14	76
18	2-naphthyl **3r**	3	19	76
19	 **3s**	6	20	58
20	 **3t**	10	7	85
21	 **3u**	3	24	71
22	 **3v**	5	39	50
23	 **3w**	5	15	62[d]
24[e]	C_6H_5 **3x**	3	15	71
25	*n*-C_7H_{15} **3y**	7	24	49
26	cyclohexyl **3z**	7	24	33

[a] General reaction conditions: α,*β*-unsaturated ketone **1a**–**z** (0.5 mmol), Oxone (amount stated in the table), dry DMF (1 mL), dry nitrogen atmosphere, room temperature (20 °C). [b] The course of these reactions was carefully followed by TLC. Reactions were stopped and worked up as soon as the ketone was consumed. [c] Isolated yield of analytically pure products **3a**–**z**. [d] Product **3w** was isolated as an inseparable mixture of diastereoisomers (10.1:1 ratio) favoring the stereochemical configuration represented in the table. [e] *trans*-Cinnamaldehyde was used as the substrate affording styryl formate **3x** as the reaction product.

(Table 3, entry 1), featuring 96% conversion in the crude reaction mixture (Table 2, entry 8).

Our Oxone-promoted reaction is more efficient on α,*β*-unsaturated methylketones that are conjugated with aromatic structures (styrene derivatives). Early phenyl halides (F, Cl, Br) are tolerated by the reaction conditions (Table 3, entries 2–5), the same as the case for trifluoromethyl groups (Table 3, entry 6). Iodo substituents were however oxidized by Oxone. α,*β*-Unsaturated methylketones with phenyl rings equipped with alkyl chains, **1g** and **1h**, are also suitable substrates, the corresponding styryl acetates, **3g** and **3h**, being isolated with acceptable yields (Table 3, entries 7 and 8). The presence of strongly deactivating/electron-withdrawing groups is equally permitted; ester (Table 3, entry 9) and amide functions, either tertiary (Table 3, entry 10) or secondary (Table 3, entry 11), allow rendering styryl acetates **3j** and **3k** in 94% and 80% yield, respectively. Nitrile or nitro groups, particularly sitting in position 2 or 4 of the phenyl ring, hamper the reaction diminishing the isolated yield of pure acetates **3l**–**o** (Table 3, entries 12–15). On the other hand, strongly activating/electron-donating hydroxyl-substituted ketone **1p** was observed to be an excellent substrate for the reaction (Table 3, entry 16). Polyaromatic derivatives, i.e. naphthyl-based ketones **1q** and **1r**, also render the corresponding vinyl acetate products smoothly and in good yield (Table 3, entries 17 and 18). The coupling constants for the olefinic protons of products **3b**–**r** are in perfect agreement with typical transoid values ($^3J_{H-H}$ = 12.6 to 12.9 Hz); hence they were assigned an (*E*)-stereochemistry for the C–C double bond.

Following this study, other substrates **1s**–**z** were prepared in order to explore the scope and limitations of our oxidation reaction in depth. In this sense, substrates consisting of two α,*β*-unsaturated methylketones moieties set on the same aromatic ring, **1s** and **1t**, underwent the reaction giving access to diacetates **3s** and **3t** (Table 3, entries 19 and 20). Interestingly, α,*β*,*γ*,*δ*-diunsaturated methylketone **1u**, prepared from *trans*-cinnamaldehyde, can be oxidized to the vinyl substituted diene **3u** in good yield, with complete retention of the (*E*,*E*) configuration of both C–C double bonds, as determined by 2D NMR experiments and from comparison with previously reported literature data[13] (Table 3, entry 21). Furthermore, other diunsaturated ketones, decorated with a chlorine or bromine halogen atom at position *γ*, **1v** and **1w**, also react to the acetate products **3v** and **3w** (Table 3, entries 22 and 23). While chlorine derivative **3v** preserves the (*E*,*Z*)-stereochemical integrity of the starting material, product **3w** was isolated as a 10.1:1 mixture of (1*E*,3*Z*) and (1*Z*,3*Z*)-isomers, favoring the first configuration. Surprisingly, cinnamaldehyde, **1x**, also underwent Baeyer–Villiger-type oxidation with Oxone, affording vinyl formate **3x** in 71% isolated yield as the major reaction product[14] (Table 3, entry 24). Finally, the ability of the reaction was investigated on aliphatic α,*β*-unsaturated methylketones. Accordingly, substrates **1y** and **1z** were prepared and subjected to the reaction conditions. The two corresponding vinyl acetate products **3y** and **3z** could be isolated from their reaction mixtures in modest yield (Table 3, entries 25 and 26). These last compounds proved to be particularly sensitive to the presence of water and were difficult to purify and isolate.

Based on the full set of results gathered in Table 3 we can state that the configuration of the α,*β*-unsaturated methylketones **1** used as starting materials is retained in the oxidized product.

In conclusion, we have developed and implemented a novel, general, and straightforward metal-free synthesis of vinyl acetates from α,*β*-unsaturated methyl ketones that occurs through a Baeyer–Villiger reaction employing Oxone as the oxidant. This transformation tolerates a wide variety of functional groups and substitution patterns, and the vinyl acetate products retain the stereochemistry of the α,*β*-unsaturated methyl ketones used as substrates. Although the mechanism of this transformation is thought to operate in agreement with other classical Baeyer–Villiger-type reactions effected by Oxone, it is being investigated in our laboratory and will be reported in due course.

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Supporting Information Available. General procedures, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for compounds **1j**, **1k**, **1v**, **1w**, and **3a**–**z**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.