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 ruthenium¹ or rhenium complexes;² the palladiumcatalyzed 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

(2) Hua, R.; Tian, X. J. Org. Chem. 2004, 69, 5782.

rendered as undesired mixtures of (*E*)- and (*Z*)-isomers. In this communication, we disclose a general transitionmetal-free synthesis of diastereopure vinyl acetates, prepared by the Baeyer–Villiger oxidation reaction⁵ of α , β -unsaturated methylketones with Oxone (potassium monopersulfate triple salt, KHSO₅·1/2 KHSO₄·1/2 K₂SO₄, Dupont registered name).⁶

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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,

 ⁽a) Ruppin, C.; Dixneuf, P. H. Tetrahedron Lett. 1986, 27, 6323.
(b) Opstal, T.; Verpoort, F. Synlett 2002, 935. (c) de Clercq, B.; Verpoort, F. Tetrahedron Lett. 2001, 42, 8959. (d) Melis, K.; Samulkiewicz, P.; Rynkowski, J.; Verpoort, F. Tetrahedron Lett. 2002, 43, 2713. (e) Opstal, T.; Verpoort, F. Tetrahedron Lett. 2002, 43, 9259. (f) Melis, K.; Opstal, T.; Verpoort, F. Leur. J. Org. Chem. 2002, 3779. (g) de Clercq, B.; Verpoort, F. Synlett 2003, 314. (i) Ye, S.; Leong, W. K. J. Organomet. Chem. 2006, 691, 1117. (j) Tan, S. T.; Fan, W. Y. Eur. J. Inorg. Chem. 2010, 4631.

⁽³⁾ Ye, C.; Xiao, J.-C.; Twamley, B.; LaLonde, A. D.; Norton, M. G.; Shreeve, J. M. *Eur. J. Org. Chem.* **2007**, 5095.

⁽⁴⁾ Soderberg, B. C.; Turbeville, M. J. Organometallics 1991, 10, 3951.

⁽⁵⁾ For recent, comprehensive reviews covering the traditional Baeyer–Villiger reaction of ketones, see: (a) Uyanik, M.; Ishihara, K. *ACS Catal.* **2013**, *3*, 513. (b) Michelin, R. A.; Sgarbossa, P.; Scarso, A.; Strukul, G. *Coord. Chem. Rev.* **2010**, *254*, 646. (c) Jiménez-Sanchidrián, C.; Ruiz, J. R. *Tetrahedron* **2008**, *64*, 2011. (d) ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Rev.* **2004**, *104*, 4105.

⁽⁶⁾ For an up to date review on the applications of Oxone in organic synthesis, see: (a) Hussain, H.; Green, I. R.; Ahmed, I. *Chem. Rev.* 2013, *113*, 3329. For recent references regarding the use of Oxone in Baeyer–Villiger oxidation reactions of ketones, see: (b) Chrobok, A. *Tetrahedron* 2010, 66, 6212. (c) Chrobok, A. *Synlett* 2011, 391. (d) Baj, S.; Chrobok, A.; Siewniak, A. *Appl. Catal. A: Gen.* 2001, *395*, 49. (e) Wang, B.; Shen, Y. M.; Shi, Y. J. Org. Chem. 2006, *71*, 9515. (f) Narender, N.; Srinivasu, P.; Kulkarni, S. J.; Raghavan, K. V. *Synth. Commun.* 2002, *32*, 279.

⁽⁷⁾ Pouraldi, A. R. Mendeleev Commun. 2010, 20, 113.

^{(8) (}a) Martínez-Castañeda, A.; Poladura, B.; Rodríguez-Solla, H.; Concellón, C.; del Amo, V. *Org. Lett.* **2011**, *13*, 3032. (b) Martínez-Castañeda, A.; Poladura, B.; Rodríguez-Solla, H.; Concellón, C.; del Amo, V. *Chem.—Eur. J.* **2012**, *18*, 5188. (c) Martínez-Castañeda, A.; Rodríguez-Solla, H.; Concellón, C.; del Amo, V. *J. Org. Chem.* **2012**, *77*, 10375.

Table 1. Initial Screening of Reagents for the Oxidation Reaction of α , β -Unsaturated Ketone **1a**^{*a*}



^{*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 ¹H NMR spectroscopy on crude reaction mixtures. ^{*c*}Conversion percentage of ketone **1a** to acetate **3a**, as determined by ¹H NMR spectroscopy on crude reaction mixtures. ^{*d*}H₂O₂ 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 ¹H NMR spectroscopy. *m*-Chloroperbenzoic acid (*m*CPBA) converted ketone 1a to a mixture consisting of epoxide 2a (9%) and the Baever-Villiger oxidation product vinvl 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 CH₃CN/H₂O 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 CH₂Cl₂/H₂O, 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 ¹H NMR spectroscopy, from comparison of the value of the ${}^{3}J_{H-H}$ coupling constants for the olefinic protons of this material with those previously reported in the literature [(*E*)-isomer: ${}^{3}J_{trans} =$ 12.8 Hz; (*Z*)-isomer: ${}^{3}J_{cis} =$ 7.4 Hz].^{1h}

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



^{*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 ¹H NMR spectroscopy on crude reaction mixtures. ^{*c*}Product **3a** was detected by ¹H 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%

^{(10) (}a) Zumbansen, K.; Döhring, A.; List, B. Adv. Synth. Catal. **2010**, 352, 1135. (b) McNulty, J.; McLeod, D. Chem.—Eur. J. **2011**, 17, 8794.

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

⁽¹²⁾ See Supporting Information for details.

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

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

L L		MF (dry), N ₂	0_0_	́~ _в	
	₩ R —	rt	3		
entry	R	Oxone equiv	time $(h)^b$	yield % ^c	
1	C ₆ H ₅ 3a	2	24	73	
2	4-F-C ₆ H ₄ 3b	3	21	80	
3	4-Cl-C ₆ H ₄ 3c	3	16	89	
4	$4\text{-Br-}C_6\text{H}_4 \; \mathbf{3d}$	3	17	88	
5	$3-Cl-C_6H_4$ 3e	5	24	73	
6	$4-\mathrm{CF}_3-\mathrm{C}_6\mathrm{H}_4\;\mathbf{3f}$	5	24	57	
7	4-Me-C ₆ H ₄ 3 g	3	24	68	
8	$4-\text{Et-C}_6\text{H}_4 \text{ 3n}$	3	18	92	
9	4-CO ₂ Me-C ₆ H ₄ 31	5	24	/0	
10		3	24	94	
11	^γ ^γ ^μ ^μ ^μ ^μ ^μ ³ ³	5	19	80	
12	4-CN-C ₆ H ₄ 31	5	24	45	
13	$4-NO_2-C_6H_4$ 3m	5	72	45	
14	3-NO ₂ -C ₆ H ₄ 3n	5	24	59	
15	2-NO ₂ -C ₆ H ₄ 30	5	48	49	
16	3-OH-C ₆ H ₄ 3 p	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	× O _{3u}	3	24	71	
22		5	39	50	
23	Br 3w	5	15	62^d	
24^{e}	C_6H_5 3x	3	15	71	
25	<i>n</i> -C ₇ H 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 trifluor-omethyl 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 **31–o** (Table 3, entries 12–15). On the other hand, strongly activating/electron-donating hydroxylsubstituted 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 $({}^{3}J_{H-H} = 12.6$ 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, $\alpha, \beta, \gamma, \delta$ -diunsaturated methylketone **1u**, prepared from *trans*-cinnamaldehyde, can be oxidized to the vinvl substituted diene **3u** in good vield, 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 data¹³ (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 (1E,3Z) and (1Z,3Z)-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 product¹⁴ (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 ¹H and ¹³C 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.

⁽¹³⁾ Dudnik, A. S.; Schwier, T.; Gevorgyan, V. *Tetrahedron* **2009**, *65*, 1859.

⁽¹⁴⁾ Syper, L. Tetrahedron 1987, 43, 2853.

The authors declare no competing financial interest.