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Phosphine-Catalyzed Synthesis of 1,3-Dioxan-4-ylidenes

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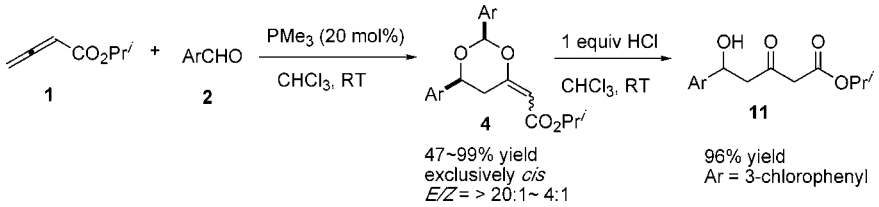
ABSTRACT



A phosphine-catalyzed reaction of an allenoate with aldehydes furnished (2,6-diaryl-[1,3]dioxan-4-ylidene)-acetates 4 in excellent to moderate yields with complete diastereoselectivity and high *E*/*Z*-selectivities. Upon removal of the acetal functionality in this domino reaction product 4, *δ*-hydroxy-*β*-ketoester 11 was obtained. The reported vinylphosphonium-based approach provides a new way to achieve a synthesis of *δ*-hydroxy-*β*-ketoesters that differs from the classical dianion-based approach.

Catalysis employing phosphines and amines as nucleophilic triggers has emerged as a rapidly growing area of synthetic organic chemistry. In particular, phosphine catalysis of allenoates and butynoates has proven to be useful for the development of new annulation reactions providing various carbo- and heterocycles.[1] Despite the abundance of coupling reactions between allenes and various electrophiles under nucleophilic catalysis, there exist no reports on phosphine-catalyzed reactions between allenes and aldehydes. As part of a program focused on the development of organic phosphine-mediated annulation reactions to form heterocycles,[2] we report herein the first phosphine-catalyzed reaction of aldehydes with allenoates to produce 2,6-disubstituted-1,3-dioxan-4-ylidene-acetates.

In an effort to expand the synthetic scope of previously reported phosphine catalyzed [3 + 2] cycloadditions, we explored the reactivity of allenoates with aldehydes.[3] On the basis of the reaction of *N*-tosylimines to form dihydropyrroles[4] we expected to obtain dihydrofuran adducts. Contrary to our expectations, dioxanylidenes **3*E*** and **3*Z***[5] were obtained in 74% yield with exclusive *cis*-diastereoselectivity and high *E*/*Z*-selectivity (*E*/*Z* = 8:1) upon mixing ethyl allenoate (**1a**) with 4-pyridinecarboxaldehyde (**2a**) in the presence of 20

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(1) For a review, see: (a) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535 and references therein. (b) Jung, C.-K.; Wang, J.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4118. (c) Wang, J.-C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5855. (d) Wang, J.-C.; Ng, S.-S.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 3682. (e) Du, Y.; Lu, X. *J. Org. Chem.* **2003**, *68*, 6463. (f) Kuroda, H.; Tomita, I.; Endo, T. *Org. Lett.* **2003**, *5*, 129. (g) Du, Y.; Lu, X.; Yu, Y. *J. Org. Chem.* **2002**, *67*, 8901. (h) Lu, C.; Lu, X. *Org. Lett.* **2002**, *4*, 4677. (i) Lu, B.; Davis, R.; Joshi, B.; Reynolds, D. W. *J. Org. Chem.* **2002**, *67*, 4595. (j) Ung, A. T.; Schafer, K.; Lindsay, K. B.; Pyne, S. T.; Amornraksa, K.; Wouters, R.; Van der Linden, I.; Biesmans, I.; Lesage, A. S. J.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **2002**, *67*, 227. (k) Kumar, K.; Kapoor, R.; Kapur, A.; Ishar, M. P. S. *Org. Lett.* **2000**, *2*, 2023. (l) Kumar, K.; Kapur, A.; Ishar, M. P. S. *Org. Lett.* **2000**, *2*, 787. (m) Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 7595.

(2) Zhu, X.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716.

(3) Reaction of ethyl 2,3-butadienoate with aldehydes in the presence of DABCO gave the normal Baylis−Hillman adducts. See: Tsuboi, S.; Kuroda, H.; Takatsuka, S.; Fukawa, T.; Sakai, T.; Utaka, M. *J. Org. Chem.* **1993**, *58*, 5952.

(4) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 3461.

(5) The connectivity and relative stereochemistry of these compounds were confirmed by X-ray crystallographic analysis. Crystallographic data for **3-*E*** and **3-*Z*** have been deposited with the Cambridge Crystallographic Data Centre as supplementary numbers CCDC 250757 and 250758. CCDC 250757 and 250758 contain the supplementary crystallographic data for this paper. These data can be obtained online free of charge (or from the Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB2 1EZ, U.K.; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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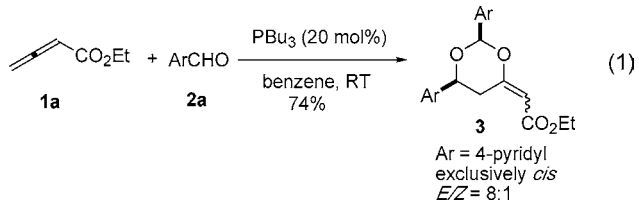
Table 1. Effect of Alkyl Group of Allenoates **1** on Formation of ([1,3]Dioxan-4-ylidene)-acetates **3**[a]

entry	R	3	yield (%)[b]	*E*/*Z* ratio[c]
1	1-naphthyl (**1b**)	**3b**	0	n/a
2	phenyl (**1c**)	**3c**	tr	n/a
3	2,2,2-trifluoroethyl (**1d**)	**3d**	0	n/a
4	2-fluoroethyl (**1e**)	**3e**	22	7:1
5	benzyl (**1f**)	**3f**	34	n/a
6	methyl (**1g**)	**3g**	50	8:1
7	ethyl (**1a**)	**3a**	37	9:1
8	isobutyl (**1h**)	**3h**	68	8:1
9	neopentyl (**1i**)	**3i**	68	8:1
10	2-trimethylsilylethyl (**1j**)	**3j**	71	8:1
11	isopropyl (**1k**)	**3k**	72	8:1
12	trimethylsilylmethyl (**1l**)	**3l**	75	8:1
13	isopropyl (**1k**)	**3k**	87[d]	8:1
14	*tert*-butyl (**1m**)	**3m**	63	10:1

[a] See Supporting Information for experimental procedure. [b] Isolated yields. [c] *E*/*Z* stereoisomer ratio determined on the basis of isolated yields. [d] 10 equiv of 3-chlorobenzaldehyde was used.

mol % tributylphosphine in benzene at room temperature [eq 1].



(1)

Though the reaction remained exclusively *cis*-stereoselective as well as highly *E*-selective for a variety of aromatic aldehydes, the product yields decreased significantly when more electron-rich aromatic aldehydes were used. For example, using the conditions in eq 1, 3-chlorobenzaldehyde and benzaldehyde provided 28% and no product, respectively. To expand the practical use of this transformation, optimized experimental conditions were developed. Trimethylphosphine provided the highest product yields among many commercially available phosphines.[6] Solvent studies demonstrated that a variety of common organic solvents afforded higher product yields than benzene.[6] Among them, chloroform was the best solvent, providing **3** in 94% yield with an improved *E*/*Z* ratio (9:1).

The yield of the reaction was augmented dramatically by tuning the electronic and steric properties of the alkoxy group of the allenoate (Table 1).[7] 3-Chlorobenzaldehyde was employed as a probe electrophile since it provided enough product to be isolated when reacted with ethyl allenoate while

(6) For detailed information, see Supporting Information.

(7) For the preparation of alkyl allenoates **1**, see Supporting Information.

Table 2. Synthesis of Isopropyl (2,6-Diaryl-[1,3]dioxan-4-ylidene)-acetates **4** from Isopropyl 2,3-Butadienoate and Aldehydes[a]

entry	R	product	yield (%)[b]	*E*/*Z* ratio[c]
1	4-pyridyl (**2a**)	**4a**	99	8:1
2	3-pyridyl (**2c**)	**4c**	96	9:1
3	2-pyridyl (**2d**)	**4d**	47	4:1
4	4-$CF_3C_6H_4$ (**2e**)	**4e**	99	7:1
5[d]	3-$CF_3C_6H_4$ (**2f**)	**4f**	90	8:1
6	2-$CF_3C_6H_4$ (**2g**)	**4g**	65	6:1
7	4-$NO_2C_6H_4$ (**2h**)	**4h**	84	8:1
8	3-$NO_2C_6H_4$ (**2i**)	**4i**	97	7:1
9	4-CNC_6H_4 (**2j**)	**4j**	99	7:1
10	3-CNC_6H_4 (**2k**)	**4k**	98	7:1
11	3-ClC_6H_4 (**2b**)	**3k**	87	8:1
12	2-ClC_6H_4 (**2l**)	**4l**	64	8:1
13	3-FC_6H_4 (**2m**)	**4m**	77	14:1
14	Ph (**2n**)	**4n**	54[e]	only *E*[f]
15	3-$MeOC_6H_4$ (**2o**)	**4o**	47	only *E*[f]
16	4-MeC_6H_4 (**2p**)	**4p**	tr	n/a
17	*n*-propyl (**2q**)	**4q**	0	n/a

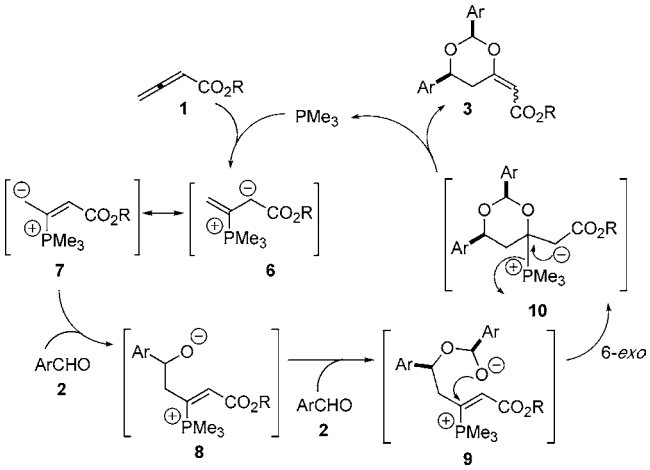
[a] See Experimental Section for experimental procedure. [b] Isolated yields. [c] *E*/*Z* stereoisomer ratio determined on the basis of isolated yields. [d] 95% of excess aldehyde was recovered. [e] 3 equiv Na_2CO_3 was added. [f] No minor isomer was isolated.

leaving ample room for improvement (37%, Table 1, entry 7). Electron-deficient alkyl or aryl groups proved detrimental to the reaction (Table 1, entries 1−4). This observation stands in contrast with the enhanced reactivity of acrylates bearing electron-deficient alkyl or aryl groups in the Baylis−Hillman reaction.[8] Use of sterically demanding and electron-rich substituents led to improved product yields (Table 1, entries 8−14). An exception to this general trend was observed for the benzyl and methyl groups (Table 1, entries 5 and 6). Extreme steric hindrance appeared to diminish product formation only to a small extent (Table 1, entry 14). From these results we speculate that steric factors are less important and product formation is governed by the allenoate electron density. Despite the optimal chemical yields obtained with trimethylsilylmethyl allenoate (Table 1, entry 12), we elected to use the more economical isopropyl allenoate for further studies. The use of a larger excess of aldehyde (10 equiv) led to a moderate increase in product yields (Table 1, entry 13). When an excess of allenoates was used, a mixture of oligomeric products that contained more than 1 equiv of allenoate formed.

Using conditions optimized for the formation of **3k**, we prepared various dioxanylidenes (Table 2). Pyridyl aldehydes as well as benzaldehydes bearing electron-withdrawing

(8) For examples, see: (a) Perlmutter, P.; Puniani, E.; Westman, G. *Tetrahedron Lett.* **1996**, *37*, 1715. (b) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219. (c) Lee, W.; Yang, K.; Chen, K. *Chem. Commun.* **2001**, 1612.

Scheme 1. Mechanistic Proposal for Formation of 1,3-Dioxan-4-ylidene **3**



groups afforded the desired dioxanylidenes in 77−99% yield (Table 2, entries 1−13), with the exception of *ortho*-substituted benzaldehydes (Table 2, entries 3, 6, and 12). The less reactive electron-rich benzaldehydes afforded moderate reaction yields (Table 2, entries 14 and 15). In the case of *p*-tolualdehyde only trace amounts of products were detected in the ^{1}H NMR of the crude reaction mixtures (Table 2, entry 16). Butyraldehyde was recalcitrant to the reaction conditions (Table 2, entry 17). The reaction was completely diastereoselective. Only 2,6-*cis*-disubstituted-1,3-dioxan-4-ylidenes were obtained for all substrates tested. The *E*/*Z*-selectivity remained in the range of >20:1 to 7:1, with the exception of 2-pyridinecarboxaldehyde (4:1, Table 2, entry 3) and 2-trifluoromethylbenzaldehyde (6:1, Table 2, entry 6).

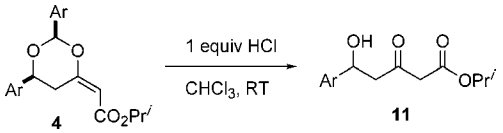
When dihydrofuran **5** was independently synthesized[9] and subjected to the optimized reaction conditions, no trace of dioxanylidene **3k** was detected, and dihydrofuran **5** was recovered in 98% yield [eq 2]. This excludes the possibility that the expected dihydrofuran **5** is an intermediate en route to the final dioxanylidene product.

Based on this observation, we rationalize that the formation of **3** arises through the γ-addition of the vinylphosphonium salt **6** ↔ **7** to an aldehyde to form **8** (Scheme 1). Adduct **8** incorporates another equivalent of aldehyde to produce **9**. The allowed 6-*exo* cyclization[10] of intermediate **9** brings

(9) For the synthesis of dihydrofuran **5**, see: (a) Kolsaker, P.; Jørgensen, T.; Wøien Larsen, G. *Tetrahedron* **1974**, *30*, 3393. (b) Hudlicky, T.; Fleming, A.; Lovelace, T. C. *Tetrahedron* **1989**, *45*, 3021.

(10) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736.

Table 3. Synthesis of δ-Hydroxy-β-ketoesters **11** via Acid-Mediated Hydrolysis of ([1,3]Dioxan-4-ylidene)-acetates **4**[a]



entry	Ar	*E*/*Z* isomer	product	yield (%)[b,c]
1	Ph (**4n**)	*E*	**11a**	97
2	3-ClC_6H_4 (**3k**)	*E*	**11b**	96
3	4-CNC_6H_4 (**4j**)	*E*	**11c**	87
4	3-CNC_6H_4 (**4k**)	*E*	**11d**	88
5	3-CNC_6H_4 (**4k**)	*Z*	**11d**	88
6	4-$NO_2C_6H_4$ (**4h**)	*E*	**11e**	82
7	4-$NO_2C_6H_4$ (**4h**)	*Z*	**11e**	85
8	3-$NO_2C_6H_4$ (**4i**)	*E*	**11f**	89

[a] See Supporting Information for experimental procedure. [b] Isolated yields. [c] Yields not optimized.

about the final zwitterionic intermediate **10**, which dissociates to 1,3-dioxan-4-ylidene **3** and trimethylphosphine. The cyclization step (**9** → **10**) is similar to Evans' base-catalyzed intramolecular conjugate addition of hemiacetal alkoxides, derived from δ-hydroxy-α,β-unsaturated esters to form benzylidene acetals of β,δ-dihydroxy esters.[11] The overall reaction is reminiscent of the three-component coupling of 2 equiv of aldehyde and one acrylate to form 5-methylene-1,3-dioxan-4-ones from the attempted Baylis−Hillman reaction.[12]

The distinctive reactivity pattern exhibited by zwitterionic intermediate **6** ↔ **7** with aldehydes adds to the increasing examples of divergent reaction pathways in nucleophilic catalysis of allenoates.[1] Recently, Shi[13] and Miller[14] reported that different reaction pathways were taken when amines were employed as catalysts instead of phosphines in nucleophilic catalysis of allenoates; however, the formation of dioxanylidene is the first example in which vinylphosphonium zwitterions add to an electrophile exclusively at the γ-carbon of allenoate **1**.[15]

The synthetic utility of this reaction is further demonstrated by acid-mediated hydrolysis of the dioxane acetal. When dioxanylidenes **4** were treated with 1 equiv of HCl, δ-hydroxy-β-ketoesters **11** were obtained in 82−97% yield (Table 3).[16] Accordingly, allenoate can be viewed as a masked precursor for the acetoacetate unit. The classical process to synthesize δ-hydroxy-β-ketoesters, referred to as the Weiler alkylation, involves γ-alkylation through the dianions of acetoacetates.[17] Generation of dianions requires use of a stoichiometric amount of two strong bases, sodium hydride

(11) Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446.

(12) For examples, see: (a) Drewes, S. E.; Emslie, N. D.; Karodia, N.; Khan, A. A. *Chem. Ber.* **1990**, *123*, 1447. (b) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 4317. (c) Reference 8.

(13) Zhao, G.; Huang, J.; Shi, M. *Org. Lett.* **2003**, *5*, 4737.

(14) Evans, C. A.; Miller, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 12394.

(15) A substituent at α-carbon of allenoates can deflect the inherent reactivity pattern of nonsubstituted allenoates. For an example, see ref 2.

(16) It is noteworthy that both the *E*- and *Z*-isomer provide one δ-hydroxy-β-ketoester.

(NaH) and *n*-butyllithium (*n*-BuLi). Our approach, which consists of a combination of neutral phosphine catalysis and acid hydrolysis, provides an alternative for the construction of ubiquitous δ-hydroxy-β-ketoesters. The resulting δ-hydroxy-β-ketoesters are recurrent subunits in polyketide antitumor antibiotics.[18]

To summarize, our effort to expand the repertoire of phosphine-catalyzed annulations has led us to the discovery of a reaction of allenoates with aldehydes to form (2,6-diaryl-[1,3]dioxan-4-ylidene)-acetates in excellent to moderate yields with complete diastereoselectivity and high *E*/*Z*-selectivities. Our vinylphosphonium-based approach provides a synthesis of δ-hydroxy-β-ketoesters, differing from the classical dianion-based approaches. Future efforts will focus on examining the synthetic potential of allenoates bearing diverse substituents at the α- and γ-carbons, as well as performing the annulation in an enantioselective manner.[19]

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Supporting Information Available: Representative experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) (a) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082. (b) Caine, D. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, Chapter 1.1.

(18) *Macrolide Antibiotics. Chemistry, Biology, and Practice*; Omura, S., Ed.; Academic Press: Orlando, FL, 1984.

(19) Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836.