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Phosphine-Mediated Reaction of 3-Alkyl Allenoates and Diaryl 1,2-Diones: Efficient Diastereoselective Synthesis of Fully Substituted Cyclopentenones[†]

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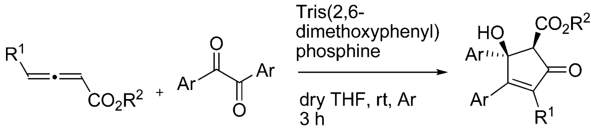
ABSTRACT



An efficient phosphine-mediated diastereoselective synthesis of substituted cyclopentenones from 3-alkyl allenoates and diaryl 1,2-diones is described.

In recent years, there has been enormous interest in the chemistry of zwitterionic species[1] largely from the standpoint of their applications in multicomponent reactions (MCRs).[2,3] In general, the zwitterions that attracted most attention are those formed by the addition of nucleophiles including nitrogen heterocycles, phosphines, and isocyanides to activated π-systems such as acetylenic esters,[4] azoesters,[5] and allenoates.[6] Investigations in a number of laboratories, including our own, have shown that zwitterions of the type mentioned above on reaction with electrophiles give rise to carbo- and heterocyclic products by 1,3- or 1,4-dipolar cycloadditions. In certain

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[†] Dedicated with best wishes to Professor Goverdhan Mehta on the occasion of his 70th birthday.

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(1) For reviews, see: (a) Acheson, R. M. *Adv. Heterocycl. Chem.* **1963**, *1*, 125. (b) Winterfeidt, E. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 423. (c) Huisgen, R. In *Topics in Heterocyclic Chemistry*; Castle, R., Ed.; John Wiley and Sons: New York, 1969; Chapter 8, p 223. (d) Nair, V.; Menon, R. S.; Sreekanth, A. R.; Abhilash, N.; Biju, A. T. *Acc. Chem. Res.* **2006**, *39*, 520.

(2) For general reviews on MCRs, see: (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3168. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (c) Scheffelaar, R.; Ruijter, E.; Orru, R. V. A. Multicomponent Reaction Design Strategies: Towards Scaffold and Stereochemical Diversity. *Top. Heterocycl. Chem.* **2010**, *25*, 95. (d) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (e) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133.

(3) For review and selected reports, see: (a) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899. (b) Nair, V.; Babu, B. P.; Varghese, V.; Sinu, C. R.; Paul, R. R.; Anabha, E. R.; Suresh, E. *Tetrahedron Lett.* **2009**, *50*, 3716. (c) Nair, V.; Deepthi, A.; Beneesh, P. B.; Suresh, E. *Synthesis* **2006**, 1443. (d) Nair, V.; Devipriya, S.; Suresh, E. *Tetrahedron* **2008**, *64*, 3567. (e) Yavari, I.; Mirzaei, A.; Moradi, L.; Khalili, G. *Tetrahedron Lett.* **2010**, *51*, 396. (f) Yavari, I.; Mokhtarporyani-Sanandaj, A.; Moradi, L.; Mirzaei, A. *Tetrahedron* **2008**, *64*, 5221. (g) Ma, C.; Ding, H.; Wang, Y. *Org. Lett.* **2006**, *8*, 3133. (h) Ma, C.; Yang, Y. W. *Org. Lett.* **2005**, *7*, 1343. (i) Terzidis, M. A.; Stephanidou-Stephanatou, J.; Tsoleridis, C. A.; Terzis, A.; Raptopoulou, C. P.; Psycharis, V. *Tetrahedron* **2010**, *66*, 947.

(4) (a) Diels, O.; Alder, K. *Liebigs Ann. Chem.* **1932**, *498*, 16. (b) Huisgen, R.; Morikawa, M.; Herbig, K.; Brunn, E. *Chem. Ber.* **1967**, *100*, 1094. (c) Johnson, A. W.; Tebby, J. C. *J. Chem. Soc.* **1961**, 2126. (d) Tebby, J. C.; Wilson, I. F.; Grifiths, D. V. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2133. (e) Acheson, R. M.; Plunkett, A. O. *J. Chem. Soc.* **1964**, 2676. (f) Winterfeldt, E. *Chem. Ber.* **1964**, *97*, 1952. (g) Winterfeldt, E.; Dillinger, H. J. *Chem. Ber.* **1966**, *99*, 1558. (h) Winterfeldt, E.; Schumann, D.; Dillinger, H. J. *Chem. Ber.* **1969**, *102*, 1656. (i) Dillinger, H. J.; Fengler, G.; Schumann, D.; Winterfeldt, E. *Tetrahedron* **1974**, *30*, 2553 and 2561. (j) Junjappa, H.; Saxena, M. K.; Ramaiah, D.; Lohray, B. B.; Rath, N. P.; George, M. V. *J. Org. Chem.* **1998**, *63*, 9801.

(5) (a) Huisgen, R. In *The Adventure Playground of Mechanisms and Novel Reactions: Profiles, Pathways and Dreams*; Seeman, J. I., Ed.; American Chemical Society: Washington, DC, 1994; p 62. (b) Nair, V.; Biju, A. T.; Mathew, S. C.; Babu, B. P. *Chem.—Asian J.* **2008**, *3*, 810. (c) Huisgen, R.; Blaschke, H.; Brunn, E. *Tetrahedron Lett.* **1966**, *7*, 405. (d) Brunn, E.; Huisgen, R. *Angew. Chem., Int. Ed.* **1969**, *8*, 513. (e) Mitsunobu, O. *Synthesis* **1981**, 1. (f) Hughs, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127.

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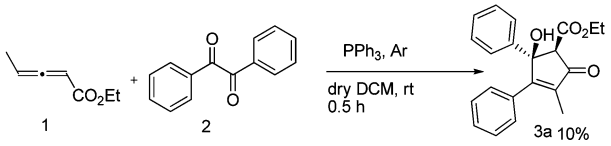
instances, the zwitterion is only an intermediate in a bond-forming reaction between two electrophiles, with the nucleophile serving just as a catalyst.

During the last 10 years, allenoate–phosphine zwitterions have been extensively investigated by several groups and their utility has been demonstrated in the construction of a variety of carbo- and heterocycles.[6,7] In the context of our work on the chemistry of zwitterions as well as 1,2-diones,[8] it was of interest to explore the reactivity of allenoate-phosphine zwitterions toward the latter, a class of uniquely reactive compounds. It is noteworthy that although annulation of allenoate-phosphine zwitterions with aldehydes has been reported by various groups,[9] their reactivity toward 1,2-diones remained unexplored, thus providing additional impetus for our work. Our studies leading to an efficient synthesis of fully substituted cyclopentenones are presented in this paper.

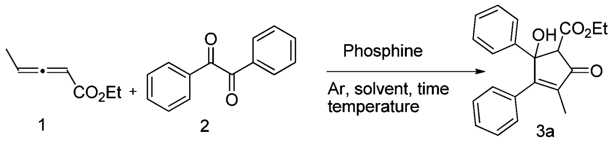
The present investigations commenced by the addition of triphenylphosphine to a solution of allenoate **1** and benzil **2** in DCM under argon atmosphere and the mixture was stirred for 30 min. The reaction mixture after column chromatography afforded a product **3a** in 10% yield (Scheme 1).

Scheme 1. Reaction of Ethyl Penta-2,3-dienoate with Benzil



The product was characterized using conventional spectroscopic methods, and conclusive evidence for its structure and stereochemistry was derived from single-crystal X-ray analysis of the analogous compound **3b** (vide infra) (Figure 1). In view of the surprising result and the fact that cyclopentenones are important compounds, it was obligatory to pursue the reaction in some detail. The reaction was optimized[10] by varying solvent, phosphine, temperature, and time; the results are presented in Table 1.

Table 1. Optimization of Reaction Conditions



entry	solvent	phosphine	temp (°C)	time (h)	yield (%)
1	DCM	PPh_3	rt	0.5	10
2	DCM	PPh_3 (5 mol %)	rt	0.5	trace
3	DCM	PPh_3	50	0.5	5
4	DCM	PPh_3	0 to rt	0.5	8
5	DCE	PPh_3	rt	0.5	5
6	$CHCl_3$	PPh_3	rt	1	trace
7	DCM	PMe_3	rt	12	
8	DCM	PBu_3	rt	0.5	25
9	DCM	$P(2\text{-}CH_3C_6H_4)_3$	rt	24	
10	DCM	TDMPP[a]	rt	4	45
11	DCM	P(Cy)$_3$	rt	4	33
12	DCM	$P(C_6F_5)_3$	rt	24	
13	THF	TDMPP[a]	rt	3	94
14	toluene	TDMPP[a]	rt	16	20

[a] TDMPP = tris(2,6-dimethoxyphenyl)phosphine.

Subsequent investigations revealed that the reaction was general with respect to different acyclic 1,2-diones and allenoates, and the results are summarized as follows (Table 2).

The reaction appears to be working well with unsymmetrical diaryl 1,2-diones, and an example using 1-(4-bromophenyl)-2-phenylethane-1,2-dione is shown in Scheme 2. However, as expected, the reaction yielded two regioisomers as inseparable mixture in 1:0.88 ratio.

The reaction may be rationalized by the following mechanistic postulate (Scheme 3). Conceivably, the first step is the nucleophilic addition of triarylphosphine to allene ester resulting in the formation of a 1,3-dipolar zwitterion. The latter then attacks a carbonyl group of the dione forming **C**. This species loses a molecule of water to afford a cationic intermediate **D**. Addition of water to the latter followed by cyclization and elimination of phosphine delivers **3a**.

Our subsequent studies showed that the reaction afforded 2-alkylidenetetrahydrofuran[11] as the major product, when triphenylphosphine was used as the catalyst with THF as solvent at room temperature. When the

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(6) For reviews, see: (a) Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140. (b) Yu, S.; Ma, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 2. (c) Zhao, Q.-Y.; Lian, Z.; Wei, Y.; Shi, M. *Chem. Commun.* **2012**, *48*, 1724. (d) Cowen, B. J.; Miller, S. J. *Chem. Soc. Rev.* **2009**, *38*, 3102. (e) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (f) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035. (g) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535.

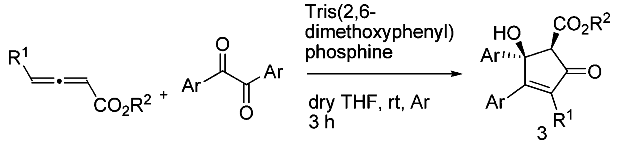
(7) For selected recent reports, see: (a) Xiao, H.; Chai, Z.; Cao, D.; Wang, H.; Chen, J.; Zhao, G. *Org. Biomol. Chem.* **2012**, *10*, 3195. (b) Chen, X.-Y.; Lin, R.-C.; Ye, S. *Chem. Commun.* **2012**, *48*, 1317. (c) Chen, X.-Y.; Ye, S. *Eur. J. Org. Chem.* **2012**, 5723. (d) Steurer, M.; Jensen, K. L.; Worgull, D.; Jørgensen, K. A. *Chem.—Eur. J.* **2012**, *18*, 76. (e) Wang, D.; Wei, Y.; Shi, M. *Chem. Commun.* **2012**, *48*, 2764. (f) Wang, Y.; Yu, Z.-H.; Zheng, H.-F.; Shi, D.-Q. *Org. Biomol. Chem.* **2012**, *10*, 7739. (g) Na, R.; Jing, C.; Xu, Q.; Jiang, H.; Wu, X.; Shi, J.; Zhong, J.; Wang, M.; Benitez, D.; Tkatchouk, E.; Goddard, W. A., III; Guo, H.; Kwon, O. *J. Am. Chem. Soc.* **2011**, *133*, 13337. (h) Wang, T.; Ye, S. *Org. Biomol. Chem.* **2011**, *9*, 5260. (i) Szeto, J.; Sriramurthy, V.; Kwon, O. *Org. Lett.* **2011**, *13*, 5420. (j) Fujiwara, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 12293.

(8) (a) Nair, V.; Paul, R. R.; Suresh, E. *Synthesis* **2010**, 3741. (b) Nair, V.; Vidya, N.; Abhilash, K. G. *Org. Biomol. Chem.* **2008**, *6*, 1738. (c) Nair, V.; Pillai, A. N.; Suresh, C. H. *Chem.—Eur. J.* **2008**, *14*, 5851. (d) Nair, V.; Biju, A. T.; Abhilash, K. G.; Menon, R. S.; Suresh, E. *Org. Lett.* **2005**, *7*, 2121. (e) Nair, V.; Pillai, A. N.; Menon, R. S.; Suresh, E. *Org. Lett.* **2005**, *7*, 1189.

(9) (a) Zhu, X.-F.; Henry, C. E.; Wang, J.; Dudding, T.; Kwon, O. *Org. Lett.* **2005**, *7*, 1387. (b) Zhu, X.-F.; Schaffner, A.-P.; Li, C. R.; Kwon, O. *Org. Lett.* **2005**, *7*, 2977. (c) Ma, R.; Xu, S.; Tang, X.; Wu, G.; He, Z. *Tetrahedron* **2011**, *67*, 1053. (d) Xu, S.; Zhou, L.; Ma, R.; Song, H.; He, Z. *Org. Lett.* **2010**, *12*, 544. (e) Xu, S.; Zhou, L.; Zeng, S.; Ma, R.; Wang, Z.; He, Z. *Org. Lett.* **2009**, *11*, 3498. (f) Xu, S.; Zhou, L.; Ma, R.; Song, H.; He, Z. *Chem.—Eur. J.* **2009**, *15*, 8698.

(10) It may be noted that the reaction proceeded smoothly when a stoichiometric amount of phosphine was used. The catalytic reaction is very slow, and it suffers from side reactions.

Table 2. Substrate Scope



entry	Ar	R^1	R^2	product	yield (%)
1	phenyl	$-CH_3$	$-C_2H_5$	**3a**	94
2	4-fluorophenyl	$-CH_3$	$-C_2H_5$	**3b**	96
3	4-chlorophenyl	$-CH_3$	$-C_2H_5$	**3c**	93
4	4-bromophenyl	$-CH_3$	$-C_2H_5$	**3d**	90
5	4-methylphenyl	$-CH_3$	$-C_2H_5$	**3e**	92
6	4-methoxyphenyl	$-CH_3$	$-C_2H_5$	**3f**	88
7	2-thienyl	$-CH_3$	$-C_2H_5$	**3g**	81
8	2-furoyl	$-CH_3$	$-C_2H_5$	**3h**	65
9	naphthyl	$-CH_3$	$-C_2H_5$	**3i**	93
10	phenyl	$-C_6H_5$	$-C_2H_5$	**3j**	81
11	4-methylphenyl	$-C_6H_5$	$-C_2H_5$	**3k**	92
12	4-fluorophenyl	$-C_6H_5$	$-C_2H_5$	**3l**	94
13	phenyl	$-CH_3$	$-C(CH_3)_3$	**3m**	82
14	4-fluorophenyl	$-CH_3$	$-C(CH_3)_3$	**3n**	83
15	4-methylphenyl	$-CH_3$	$-C(CH_3)_3$	**3o**	78

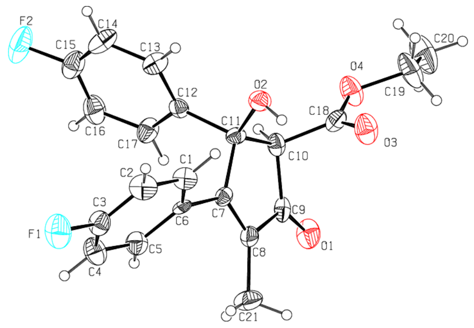
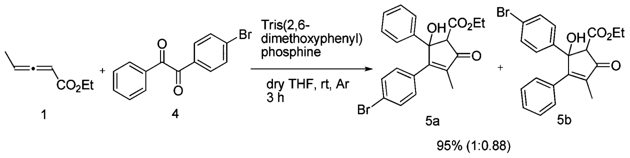
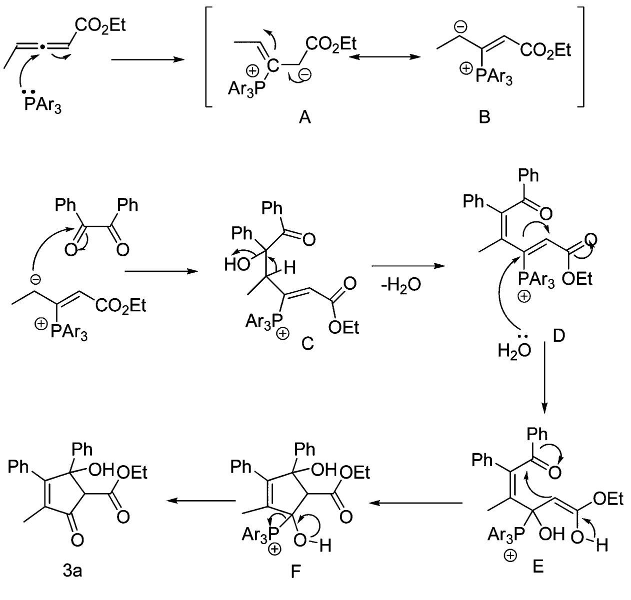


Figure 1. ORTEP diagram of **3b**.

Scheme 2. Reaction of Ethyl Penta-2,3-dienoate with 1-(4-Bromophenyl)-2-phenylethane-1,2-dione

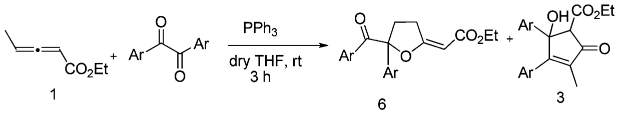


Scheme 3. Proposed Mechanism



Ar = 2,6-dimethoxyphenyl

Scheme 4

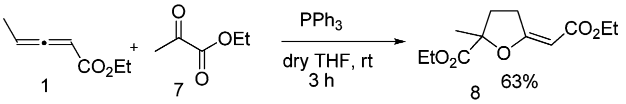


Ar = phenyl; 6a (56%) + 3a (12%)
Ar = 4-methylphenyl; 6b (77%) + 3e (2%)
Ar = 4-fluorophenyl; 6c (35%) + 3b (20%)
Ar = 2-thienyl; 6d (63%)
Ar = naphthyl; 6e (40%) + 3i (9%)

reaction was conducted in solvents such as toluene, dioxane, or xylene, the same product was obtained in low yield. In this context, it may be recalled that He and coworkers have reported the annulation of phosphine-γ-alkyl allenoate zwitterion to aldehydes to afford 2-alkylidenetetrahydrofurans.[9f] A few examples using representative 1,2-diones and ethyl penta 2,3-dienoate are given in Scheme 4.

Interestingly, the reaction with ethyl pyruvate under the same condition afforded 2-alkylidenetetrahydrofuran derivative exclusively (Scheme 5).

Scheme 5



In conclusion, we have encountered a novel annulation of allenoate–phosphine zwitterion with acyclic 1,2-diones resulting in the formation of substituted cyclopentenone

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(11) The *E* geometry of the double bond in 2-alkylidenetetrahydrofurans was ascertained by comparing the chemical shift values of analogous compounds reported.[9f] Further support for the assignment was accrued by NOE studies of compound **6d**.

derivatives. It is noteworthy that 4-hydroxycyclopentene-1-ones are of pharmacological importance and are embedded in natural products such as prostaglandins.[12] In addition, a number of natural and synthetic 4-hydroxy cyclopentene-1-ones are useful crop protection agents.[12c,13] It may also be mentioned that cyclopentenones have found use in the construction of polysubstituted aromatic hydrocarbons,[14] isotruxenones,[15] and diquinanes.[16]

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Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For reviews on prostaglandins, see: (a) Pace-Asciak, C.; Granström, E. *Prostaglandins and Related Substances*; Elsevier: New York, 1983. (b) Nicolaou, A.; Kokotos, G. Prostanoids. In *Bioactive Lipids*; Oily Press: Bridgwater, 2004; p 197. (c) *Römpp Lexikon Naturstoffe*; Fugmann, B., Lane-Fugmann, S., Steglich, W., Eds.; Thieme: Stuttgart, 1997. (d) Bindra, J. S. The Synthesis of Prostaglandins. In *Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley & Sons, Inc.: Hoboken, 2007; Vol. 4, Chapter 4.

(13) (a) *Molecular Action of Insecticides on Ion Channels*; American Chemical Society: Washington, DC, 1995; ACS Syp. Ser. 591, p 2643. (b) *Handbook of Pesticide Toxicology*; Hayes, W. J., Ed.; Academic Press: New York, 1991; p 585.

(14) Holtz, E.; Köhler, V.; Appel, B.; Langer, P. *Eur. J. Org. Chem.* **2005**, 532.

(15) Yang, J.-S.; Huang, H.-H.; Lin, S.-H. *J. Org. Chem.* **2009**, *74*, 3974.

(16) Romero, J. M. L.; Sapmaz, S.; Fensterbank, L.; Malacria, M. *Eur. J. Org. Chem.* **2001**, 767.

The authors declare no competing financial interest.